Virus-induced changes in mitochondrial bioenergetics as potential targets for therapy[☆]

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ABSTRACT

Infectious diseases such as those caused by virus, account for a vast proportion of deaths worldwide. Re-emerging aspects of host–virus interactions in recent literature include the vital role played by host metabolism on viral replication and the pro-active participation of mitochondria in this process. Different viruses use distinctive strategies to modulate mitochondrial bioenergetics and enhance viral replication. As a result, energy yielding metabolic pathways are programmed to provide both energy and biosynthetic resources to drive viral protein synthesis and produce infectious particles. Therefore, metabolic antagonists may prove important not only to outline efficient therapy strategies but also to shed light on the pathogenesis of viral infections.

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1. Introduction

Infectious diseases still account for a vast proportion of deaths and disabilities worldwide. In low-income countries they are considered a higher burden if compared to high-income countries, where non-communicable diseases are the main cause of death. Estimates of the burden of infectious diseases at regional or global levels can mask the importance of specific infections on particular populations. For instance, the burden of viral infections such as dengue fever varies with environmental and other conditions and can rapidly assume epidemic proportions. Additionally, chronic diseases carrying significant association with infectious pathogens, such as hepatocellular carcinoma (e.g., Hepatitis B or C virus infections) are not considered as infectious diseases (Saker et al., 2004). As a consequence, the burden of infectious diseases seems to be even higher if these aspects are considered.

The crucial role played by the host metabolism on viral replication and the infectious process is a re-emerging aspect of host–virus interactions in the recent literature. Because viruses do not have mechanisms for channeling energy, they must parasitize living cells to bring viral information into function. Indeed, about 60 years ago Ackermann and colleagues searched for enzyme systems and pathways of the host cells which could be potentially sequestered for viral replication/biogenesis and thus used as targets for treatment (Ackermann and Klernschmidt, 1951; Ackermann and Johnson, 1953). Their pioneer observations revealed the physical and biochemical relationship between mitochondria and Influenza A and mitochondria and herpes viruses. By utilizing mitochondrial inhibitors and uncouplers, they observed significantly lower viral yield and proposed that viral propagation is an oxidative process which requires functional mitochondria. Currently, it is widely accepted that hosts provide both energy and biosynthetic precursors for viral protein synthesis and assembly.

The virus cycle is a dynamic process that involves different organelles; different viruses have developed distinctive replication strategies. In fact, aside from their role in the apoptotic process, mitochondria seem to actively participate in the replication process. In this review, we cover some aspects related to the modulation of mitochondrial bioenergetics during viral infection and the impact of virus-induced mitochondrial dysfunction on cellular metabolism. We also address potential metabolic targets for therapeutics.

2. Organelle function: basic overview of mitochondrial ATP synthesis

Although some ATP is synthesized by glycolysis in the cytoplasm of eukaryotic cells, most cellular ATP is synthesized by membrane-bound protein complexes, which comprise the electron transport system (ETS) confined to mitochondria. Electron transport occurs through protein complexes located in the inner mitochondrial
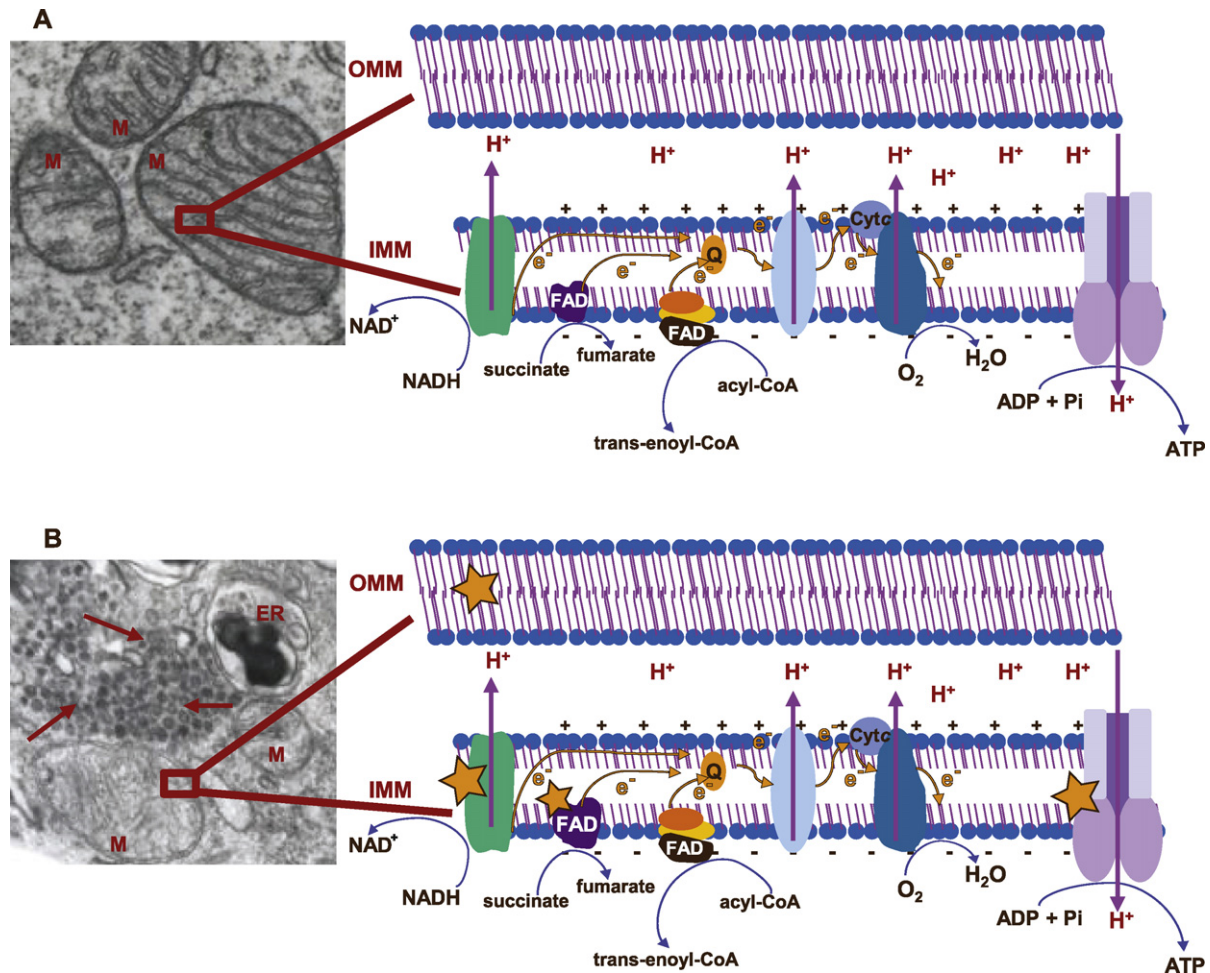
Fig. 1. Mitochondrial respiratory chain and oxidative phosphorylation: (a) electron transmission micrograph of human hepatic cells showing mitochondrion (M) with electron dense cristae; (b) electron transmission micrograph of human hepatic cells infected with dengue virus (electron dense particles; arrows). Viral particles (red arrows) localize close to mitochondrion (M) and to endoplasmic reticulum (ER). The illustrations in the right represent a section of the mitochondrial membranes: IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; in light green, complex I; in purple, complex II; in black, acyl-CoA dehydrogenase; the orange circle labeled with Q, ubiquinone; in light blue, complex III; the blue circle labeled with Cyt c, cytochrome c; in dark blue, complex IV; in light purple, ATP synthase. The e- represents the electrons. Orange stars represent potential sites of viral modulation of mitochondrial bioenergetics for HBV and HCV (OMM); Sindbis Virus, HCMV and HCV (complex I); Sindbis virus (complex II); HCV (complex V).

membranes (IMM), which contain prosthetic groups (flavins, iron-sulfur groups, heme, and cooper ions) capable of accepting or donating one or more electrons. Electrons are transferred from substrates to molecular oxygen, the final electron acceptor. Complex I (NADH ubiquinone oxidoreductase) accepts electrons from reduced nicotinamide adenine dinucleotide (NADH), while complex II (succinate dehydrogenase) accepts electrons from reduced flavin adenine dinucleotide ($FADH_2$). Oxidation of NADH and $FADH_2$ is followed by reduction of ubiquinone. Electron transfer flavoprotein (ETFP), a protein involved in fatty acid oxidation, also oxidizes $FADH_2$ by transferring of electrons to ubiquinone. Complex III (ubiquinol-cytochrome c oxidoreductase) is responsible for the transfer of electrons from ubiquinone to cytochrome c. Complex IV (cytochrome oxidase) promotes the oxidation of cytochrome c and reduction of molecular oxygen to water (Fig. 1). Respiratory complexes are organized into entities called supercomplexes, which define respiration efficiency and subunit stability (D'Aurelio et al., 2006). The energy derived from the transfer of electrons is used by complexes I, III and IV to move protons across the inner membrane and to generate a gradient of protons. The electrochemical energy created by the combined effects of pH gradient (ΔpH) across the inner mitochondrial membrane and transmembrane electrical potential ($\Delta\Psi m$), called the proton motive force, drives ATP

synthesis from ADP and Pi as protons move back to the mitochondrial matrix through complex V (ATP synthase) channel. Electron transfer in mitochondria is thus coupled to oxidative phosphorylation of ADP or ATP synthesis. The stoichiometry of the coupling efficiency is measured by the ratio of Pi incorporated to ADP to moles of O_2 consumed (P/O). Several factors affect the coupling of electron transfer – and therefore oxygen consumption – to ATP synthesis, including alterations in inner membrane permeability, the activity of uncoupling proteins, slip or leak of protons and the activity of carrier transporters (Brown, 1992). Mitochondria can be easily damaged, with severe consequences to the cell function. For instance, pathological conditions that distress mitochondrial membrane permeability (MMP) affect oxidative phosphorylation and mitochondrial ATP synthesis. Therefore, respiratory states, systematized by Chance and Williams (1956), and respiratory control ratios and P/O ratios, measured in intact and permeabilized cells, are useful for the evaluation of mitochondria (dys)function in different pathologies (Pesta and Gnaiger, 2012), including viral infections. These measurements can be used for the evaluation of the phosphorylation and electron transport systems, the activities of respiratory complexes, and coupling efficiency, and represent important tools for investigating viral effects on mitochondrial functions and understanding the pathogenesis of viral diseases.

3. Organelle pathology: mitochondrial bioenergetics during viral infections

Mitochondria are implicated in several host and viral responses. Innate immune responses against viral infection culminate with the production of type I Interferon (IFN-α and IFN-β) and other proinflammatory cytokines and chemokines. Following infection, viral components, as double-stranded RNA (dsRNA) and single-stranded RNA and DNA, are sensed by germline-encoded pattern-recognition receptors (PRR) of the hosts. dsRNA are sensed by two classes of PRR, endossomal Toll-like receptors (TLRs) and cytoplasmic retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), RIG-I itself and melanoma differentiation associated gene 5 (MDA-5). Signal transduction from RLRs strictly depends on mitochondrial anti-viral signaling protein (MAVS) (also called IPS-1, CARDIF and VISA). MAVS associates with the outer mitochondrial membrane (OMM) and its localization is essential for antiviral immune responses (West et al., 2011). MAVS recruits several molecules to transduce downstream signaling that will culminate in the activation of NFκB and Interferon Regulatory Factors (IRF), which are critical for mounting adaptive immune responses. Viruses have developed distinct strategies to usurp MAVS signaling, and thus decreasing early innate immune responses, as observed for Hepatitis A, B and C viruses. One striking aspect of MAVS antiviral signaling is that it seems to depend on mitochondrial dynamics. Mitofusins, which regulate mitochondrial fusion, were shown to interact with MAVS, which is essential for proper antiviral responses. Cells lacking mitofusins presented a loss in ΔΨm, associated with defective anti-viral innate immune response (Koshiba et al., 2011). This indicates that mitochondria network integrity and sustained respiratory capacity are important for early anti-viral innate immune responses.

Mitochondrial control of apoptosis during viral infection is also an important aspect of innate immunity. In this regard, modulation of MMP is the central point of control of apoptosis via the intrinsic pathway. Increase in MMP, disrupts ΔΨm and affects mitochondrial bioenergetics. Viruses have developed strategies to modulate MMP and to effectively control cell death. In this regard, anti- or pro-apoptotic viral proteins co-opt host mitochondria to modulate MMP, affecting mitochondrial bioenergetics in favor of replication (Ohta and Nishiyama, 2011). Some of these proteins exhibit bcl-2 family-like functions or structures.

Virus-induced changes in mitochondrial bioenergetics as vital mechanisms to drive replication may represent early responses to viral infection. This seems to be the case of Human Cytomegalovirus (HCMV), the prototypical beta-herpes virus, which infects more than half of the global population. HCMV replication is slow in cultured cells and it must efficiently control cellular processes for biosynthesis and virion production. It has been shown that the 2.7-kb HCMV encoded RNA (β2.7) locates in the mitochondria (Reeves et al., 2007). This RNA interacts with mitochondrial complex I, protecting cells from apoptosis and maintaining cellular ATP content. An RNA-mitochondria interaction is an important strategy because it can rapidly modulate mitochondrial functions and ensure viral replication.

Recently, an intriguing observation revealed that vMIA, an antiapoptotic protein expressed by HCMV, interacts with viperin, a protein involved in anti-viral effects, and relocates the latter to mitochondria (Seo et al., 2011). This relocation reduces fatty acid β-oxidation and ATP content, resulting in actin cytoskeleton disruption, which seems to burst HCMV infection in fibroblasts. Interestingly, reduced β-oxidation stimulates viral replication, indicating that mitochondrial ATP generation by fatty acid oxidation is not essential to HCMV replication. Indeed, glutamine oxidation seems to be crucial for HCMV replication as it is used for anaplerotic reactions of the tricarboxylic acid (TCA) cycle and essential for mitochondrial ATP production (Chambers et al., 2010) (Fig. 2).

Modulation of mitochondrial functions during HCMV infection has also been suggested by metabolomics and fluxomics analyses, which have shown an enhanced metabolic flux through glycolysis and TCA cycle (Vastag et al., 2011). The enhanced TCA cycle is associated to citrate export to cytoplasm and linked to an upregulation of lipid biosynthesis necessary for viral envelopment, enlargement of the nucleus and of vesicular bodies of the infected cells (Vastag et al., 2011; Munger et al., 2008).

Another interesting aspect of HCMV-induced modulation of mitochondrial functions is that viral replication depends on mitochondrial biogenesis, which in turn depends on vMIA activity (Kaarbø et al., 2011). Mitochondrial biogenesis has been shown to be followed by increased respiratory capacity related to complex I substrates and involves enhanced PCG-1α expression.

Dengue virus infection is the most common arboviral disease and causes acute infection. Liver dysfunction is characteristic of disease severity. Although the mechanisms underlying organ dysfunction are not fully understood, alterations in lipid metabolism also seem to be involved. It has been shown that mobilization of triacylglycerol (TG) stores from lipid droplets (LD) induced by autophagy enhances β-oxidation and ensures cellular ATP levels and viral replication (Heaton and Randall, 2010). Possibly differences in the replication cycle of HCMV and dengue virus could explain the distinct effects on lipid oxidation.

Our group has also shown that mitochondrial functional alterations occur during dengue virus infection of human hepatic cells, with increased respiration uncoupled to ATP synthesis, reflected by decreased ΔΨm, ADP/O ratio and ATP content, and induction of apoptosis (El-Bacha et al., 2007). A recent study showed that TLR-3 induces a decrease in mitochondrial respiration in the same hepatic cellular model we used (Djafarzadeh et al., 2011). Since we have also shown that dengue virus infection induces an increased expression of different modulators of innate immunity, including TLR-3 (Conceição et al., 2010), one could speculate a link between liver control of innate immunity and mitochondrial bioenergetics dysfunction in dengue virus infection.

Sindbis virus, the prototypical alphavirus, causes acute encephalitis in mice and it is an interesting model for the investigation of the molecular mechanisms of encephalitis in humans. Mitochondrial bioenergetics alterations seem to participate in this process. Recently, we observed that modulation of mitochondrial function in Sindbis virus infection of mouse neuroblastoma cells, is a necessary mechanism to drive viral replication (Silva da Costa et al., 2012). Mitochondria function seemed to be improved in the beginning of infection, as shown by enhanced respiration-related to phosphorylation and also by enhanced respiratory control ratio (RCR) related to complex I substrates, which accounted for the maintenance of cellular ATP content. As infection progresses, both complex I and II-associated respiration seem to be affected, and ATP content drops. Taking into account the results shown by Kaarbø et al. (2011), both HCMV and Sindbis viruses require increased production of mitochondrial ATP to drive replication, despite the fact that HCMV is a slow replicating virus and Sindbis replication cycle is short.

Severe alterations in mitochondrial functions are also observed in chronic Hepatitis C Virus (HCV) infection, the leading cause of death from liver disease. Human cells stably expressing HCV polyprotein (Ripoli et al., 2010), present decreased routine respiration and decreased respiration uncoupled to ATP synthesis, resulting in decreased RCR. These differences might account for lower complex I activity and ATP synthase activity. OMM and contact sites between endoplasmic reticulum (ER) and mitochondria
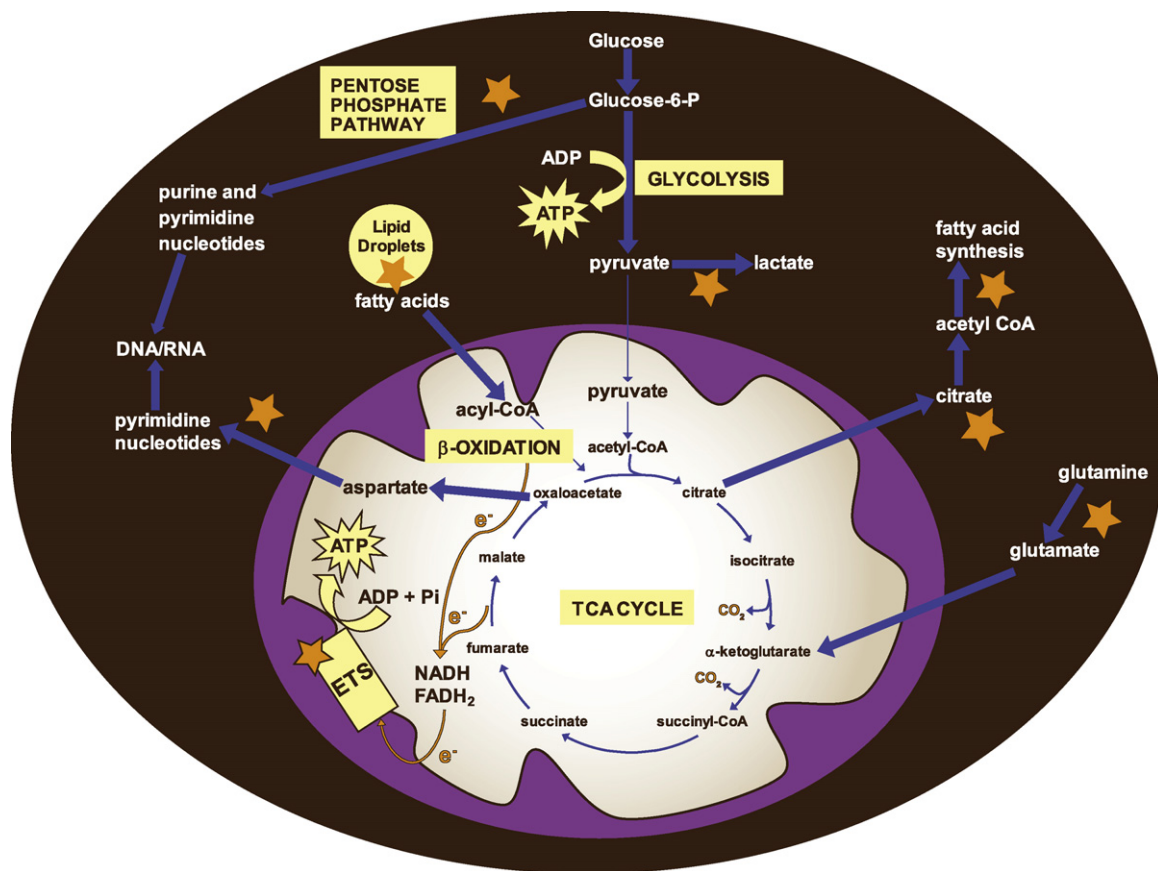
Fig. 2. Metabolic effects of viral infections: viral replication affects mitochondrial bioenergetics, which in turn affects overall energy metabolism. Stars and thick arrows represent metabolic steps stimulated by virus infection and potential metabolic targets for therapy, as described in the text. Increased fluxes through glycolysis and pentose phosphate pathway have been observed following HCMV, Mayaro and Kaposi-sarcoma viruses. Herpes simplex-1 virus stimulates pyrimidine metabolism through deviation of oxalacetate from TCA cycle; deviation of citrate from mitochondria to be used for fatty acid synthesis is a mechanism utilized by HCMV; dengue virus stimulates degradation of lipid droplet stores and increases β-oxidation; HCV infection, on the other hand, promotes decreased utilization of triacylglycerol in lipid droplets; increased entry of carbons into the TCA cycle from glutamine metabolism is observed after HCMV infection; mitochondrial electron transfer system (ETS) is affected in different ways after viral infections.

appear to be the localization of some HCV proteins (Piccoli et al., 2009), indicating that Ca^{2+} metabolism might participate in mitochondrial dysfunction.

Lastly, oxygen consumption of CD4+ lymphocytes isolated from patients infected with the human immunodeficiency virus (HIV) is significantly reduced in patients receiving anti-viral therapy, with an apparent decrease in both ETS and oxidative phosphorylation capacities (Einsiedel et al., 2010). Interestingly, anti-retroviral treatment per se causes this effect, as mitochondrial respiration of lymphocytes from patients not receiving treatment is similar to that from controls. However, metabolomics analyses of lymphocytes CD4+ have been inconclusive regarding TCA cycle modulation after HIV infection (Hollenbaugh et al., 2011).

Thus, irrespective of replication cycle and lytic and latent infections, modulation of mitochondrial bioenergetics is an important aspect of viral-induced changes in cellular metabolism, and understanding these effects may help choose adequate anti-viral therapy, and tools to follow-up treatment.

4. Cell physiology: virus-induced mitochondrial dysfunctions (effects on cellular metabolism)

The mechanisms associated to the synthesis and utilization of ATP are tightly regulated so that cellular ATP content remains constant. Alterations in the crosstalk between mitochondria and cytoplasm are observed in cancer cells, which show increased rates of ATP production via glycolysis even in the presence of high oxygen tension. Similar effects are observed in some types of viral infection, which causes cell transformation. For instance, in latent infection with Kaposi's sarcoma-associated herpes virus, decreased mitochondrial oxygen consumption is compensated by increased glycolysis (Delgado et al., 2010). Interestingly, inhibitors of glycolysis such as oxamate and 2-deoxyglucose induce apoptosis in infected cells. Glycolytic compensation has also been observed in cellular models chronically expressing HCV polyprotein, which exhibits suppressed mitochondrial functions. The increased glycolysis is mediated by HIF-1α stabilization, which not only maintains but also increases cellular ATP content (Ripoli et al., 2010). An increase in cellular ATP has also been observed following HCMV (Chambers et al., 2010) and Herpes simplex-1 virus HSV-1 infections (Abrantes et al., 2012). The significance for both viral and cellular processes of this new ATP steady-state following infection remains to be elucidated. Upregulation of glycolysis is seen even in the absence of mitochondrial alterations, as we observed in Mayaro infection, which is caused by an alphavirus as well (El-Bacha et al., 2004). It seems that glucose metabolism is altered upon increased activity of PFK-1, which not only drives ATP synthesis but also deviates glucose carbons for pentose phosphate pathway (PPP) for biosynthetic purposes. Increased flux through PPP is also seen in HCMV infected cells (Vastag et al., 2011) (Fig. 2). Functional activation of PFK-1 has also been shown after HCMV infection (Munger et al., 2006).

As previously discussed, virus infections can also affect lipid metabolism through modulation of TCA cycle. This is the case for HCMV (Vastag et al., 2011; Munger et al., 2008). HCMV infection

deviates citrate from mitochondria to the cytoplasm where it serves as substrate for ATP-citrate lyase, yielding oxalacetate and acetyl CoA. The latter serves as an indirect substrate for fatty acid synthase complex to synthesize fatty acids (Fig. 2). Indeed, by inhibiting fatty acid synthesis the authors observed lower viral production, showing that the upregulation of lipid biosynthesis is important for viral envelopment and replication. In addition to deviation of metabolic intermediates, activation of sterol regulatory element binding protein 1 (SREBP1) seems to be a key factor for lipogenesis up-regulation and HCMV proliferation (Yu et al., 2012). Striking alterations in lipid metabolism are also observed in different models of HCV infection. Cells infected with HCV (as well as liver biospsies from infected subjects), present increased accumulation of triacylglycerol, deposit in LD. LD accumulation is important for maturation of viral particles. Increased and decreased expression, respectively, of PPARγ (Lima-Cabello et al., 2011) and of PPARα (Wu et al., 2011), seem to be involved in increased lipogenesis. The association of SREBP1 expression and lipid metabolism in the case of HCV infection, on the other hand, is not clearly seen. Drugs targeting lipid metabolism, as for HCMV, show potential therapeutic applications for HCV-induced liver injury.

Modulation of TCA cycle is also observed during herpes simplex virus-1 (HSV-1) infection (Vastag et al., 2011). Fluxomics analysis show that HSV-1 infected cells deviate oxalacetate from TCA cycle and increase its conversion to aspartate for purine pyrimidine synthesis (Fig. 2). This is a very interesting finding and shows another strategy of viral replication that relies on intermediary metabolism, as observed in HCMV infection.

Moreover, viral infections induce production of reactive oxygen species (ROS) that control replication, as different viruses are able to modulate antioxidative enzymes. Increased ROS production might contribute to alterations in mitochondrial bioenergetics. Dysfunctional mitochondria, in turn, can contribute to exacerbate oxidative stress, resulting in energy collapse and cell death (Kowaltowski et al., 2009). This effect has been proposed for Sindbis virus infection and HCV infection (Silva da Costa et al., 2012; Piccoli et al., 2009). Calcium metabolism appears to be involved in ROS-induced mitochondrial oxidative stress, as shown for HCV infection (Piccoli et al., 2009), where endoplasmic reticulum (ER) actively participates in this process. Recently, calcium metabolism has also been shown to participate in HCMV induction of glycolysis, as calmodulin-dependent kinase kinase inhibition decreased glycolytic flux and halted viral replication, suggesting another possible target for therapeutics (McArdle et al., 2011). Virus-induced ROS production also links immune response to mitochondria. Increased ROS production potentiates MAVS downstream signaling to IRF-3 and NFκB, therefore, limiting viral replication. Mitophagy, the selective removal of mitochondria by macroautophagy, also attenuates ROS production by removing dysfunctional mitochondria, and is a mean to control exacerbating immune responses (West et al., 2011). The impact of mitophagy as a mechanism for controlling replication of the different viruses needs to be established.

5. Future outlook

Just as proposed for cancer cells (Smolková et al., 2011), virus infections induce a metabolic re-programming, resulting in distinctive bioenergetic phenotypes, which are crucial to drive viral replication. Therefore, metabolic antagonists may be important not only to treat viral infections but also to provide us with a better understanding of virus-modulation of host metabolism, especially the metabolic strategies used by different viruses. Functional and structural studies on the organization of mitochondrial supercomplexes and on mitochondrial network in infected cells are important aspects of mitochondrial physiology. These aspects may shed light on the viral strategies as they are all related to modulation of calcium metabolism and oxidative stress.

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