Published in final edited form as:
Front Biol (Beijing). 2014 December ; 9(6): 423–436. doi:10.1007/s11515-014-1332-0.

Functional implications of mitochondrial reactive oxygen species generated by oncogenic viruses

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Abstract

Between 15–20% of human cancers are associated with infection by oncogenic viruses. Oncogenic viruses, including HPV, HBV, HCV and HTLV-1, target mitochondria to influence cell proliferation and survival. Oncogenic viral gene products also trigger the production of reactive oxygen species which can elicit oxidative DNA damage and potentiate oncogenic host signaling pathways. Viral oncogenes may also subvert mitochondria quality control mechanisms such as mitophagy and metabolic adaptation pathways to promote virus replication. Here, we will review recent progress on viral regulation of mitophagy and metabolic adaptation and their roles in viral oncogenesis.

Keywords

mitochondria; mitophagy; virus; ROS; oncogenes

Introduction

Reactive oxygen species (ROS) are small molecules generated as by-products during normal cellular metabolism of oxygen. Cellular levels of ROS are crucial for cell fate (Pan, 2009; Martin and Barrett, 2002). In normal cells, ROS is now established to play key signaling roles in cell differentiation, autophagy and immune responses (Sena and Chandel, 2012; Ray et al., 2012). However, accumulation of intracellular ROS is potentially harmful to normal cells, causing oxidation of nucleic acids, proteins, and lipids, and can lead to oxidative stress (Cooke et al., 2003; Babusikova et al., 2013; Bernard et al., 2012; Sawada and Carlson, 1987). The deleterious effects of ROS have been associated with numerous human pathologies such as aging, cardiovascular diseases, neurodegenerative diseases and cancer (Brieger et al., 2012).

Intracellular ROS are produced in aerobic organisms as a result of enzyme reactions from various intracellular sources including peroxisomes, endoplasmic reticulum (ER) and mitochondria (Waris and Ahsan, 2006). Peroxisomes oxidize intracellular nicotinamide adenine dinucleotide phosphate (NADPH) to reduce oxygen (O_2) to superoxide (O_2^-) by membrane-associated NADPH oxidase (NOX) and toxic molecules (e.g. ethanol) to

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hydrogen peroxide (H_2O_2) by catalase. The ER oxidizes unsaturated fatty acids and xenobiotics via cytochrome P450 and b5 enzymes to produce O_2^- and H_2O_2. (Bonekamp et al.; Schrader and Fahimi, 2006). Mitochondria produce ROS through incomplete reduction of oxygen (O_2) to water (H_2O) from the electron transfer chain (ETC) and by mitochondrial enzymes such as dehydrogenases. Mitochondria are considered the chief source of intracellular ROS production because mitochondrial ROS (mROS) have been directly linked to multiple physiologies including immunity, differentiation, autophagy and metabolic adaptation (Sena and Chandel, 2012), and diverse pathological conditions such as cancer, autoimmunity and cardiovascular diseases all share common characteristics of elevated mROS (Sena and Chandel, 2012; Li et al., 2013; Turrens, 2003).

The generation of mROS is tightly regulated in primary cells. Various cell stimuli, including immunoreceptor ligation and cytokine stimulation, pathogen infection and hypoxia increase mROS levels. In addition, elevated cytosolic calcium levels and activation of phosphatidylinositol 3-kinase lead to elevated mROS. However, due to the high reactivity and toxicity of mROS, mammalian cells have evolved a number of antioxidant enzymes including superoxide dismutases, peroxiredoxins, glutathione peroxidase, and catalase to neutralize mROS (Li et al., 2013; Sena and Chandel, 2012). Furthermore, mitophagy can also downregulate mROS by removing damaged mitochondria that secrete high levels of ROS (Tal et al., 2009; Wang et al., 2012; Lee et al., 2012a).

Mitophagy is the process by which dysfunctional mitochondria are selectively eliminated by the highly conserved autophagic machinery (Jin and Youle, 2012; Novak, 2012; Youle and Narendra, 2011). The best studied mitophagy pathway is the PTEN-induced putative kinase 1 (PINK1)/Parkin-mediated pathway (Fig. 1) (Jin and Youle, 2012). Mutations in PINK1 and Parkin cause early-onset neurodegenerative disease such as juvenile Parkinson's disease (PD) (Kitada et al., 1998; Valente et al., 2004). PINK1 is a mitochondrial kinase that is imported into the matrix and the intermembrane space. In healthy polarized mitochondria, imported PINK1 is constitutively and rapidly degraded by sequential actions of mitochondrial proteases and the proteasome (Greene et al., 2012; Yamano and Youle, 2013; Jin et al., 2010). However, upon mitochondrial depolarization or damage induced by protonophores such as carbonyl cyanide 3-chlorophenylhydrazone (CCCP) or a short burst of mROS via photosensitizers (e.g. mitochondria-targeted KillerRed protein), the constitutive degradation of PINK1 is inhibited resulting in PINK1 accumulation on the outer mitochondrial membrane (Wang et al., 2012; Narendra et al., 2008), where it recruits Parkin and activates its ubiquitin ligase activity (Shiba-Fukushima et al., 2012). In recent studies, two groups independently demonstrated that PINK1 activates the enzyme activity of Parkin through PINK1-mediated ubiquitin phosphorylation at serine 65 (Kane et al., 2014; Koyano et al., 2014). Subsequently, activated Parkin ubiquitinates mitochondrial proteins mitofusin 1 and 2 (Mfn1/2), Drp1, Bcl-2 and voltage-dependent anion channel 1 (VDAC1) (Chen et al., 2010; Tanaka et al., 2010; Wang et al., 2011; Geisler et al., 2010). The adaptor protein p62/SQSTM1 is a ubiquitin-binding autophagy receptor that links ubiquitinated mitochondria to autophagosomes (Pankiv et al., 2007). However, it is unclear whether p62/SQSTM1 serves as a mitophagy receptor (Okatsu et al., 2010; Huang et al., 2011; Narendra et al., 2010), although it is plausible that p62/SQSTM1 may be required for Parkin-induced perinuclear clustering of damaged mitochondria (Okatsu et al., 2010; Narendra et al., 2010).

In addition to the PINK1/Parkin-mediated mitophagy pathway activated by mitochondrial damage, there are other mitophagy pathways that are developmentally programmed through specific receptors (Ding and Yin, 2012). For example, red blood cells (RBCs) lose their mitochondria in order to transport oxygen instead of consuming it by mitophagy (Ney, 2011; Fader and Colombo, 2006). The BH3-only protein (BOP) NIX plays an important role as a mitophagy receptor in maturing murine reticulocytes by recruiting Atg8 family members LC3 and GABARAP to damaged mitochondria (Novak et al., 2010). Also, in response to high oxidative phosphorylation activity, NIX regulates mitophagy elicited by the small GTPase Rheb (Melser et al., 2013). Another BOP member, BNIP3, also functions as a mitophagy receptor in mitophagy elicited by metabolic stress (Feng et al., 2013; Zhang and Ney, 2009). Furthermore, the mitochondrial protein FUNDC1 was reported to play a role as a mitophagy receptor in hypoxia-induced mitophagy (Fig. 1) (Liu et al., 2012). The expression of mitophagy-specific receptors are regulated during hypoxia through induction of hypoxia-inducible factor 1 (HIF-1) or suppression of microRNA-137 (Bruick, 2000; Li et al., 2014).

Hypoxia induces a change in mitochondrial redox and alters the production of mROS (Chandel et al., 1998; Guzy et al., 2005; Hamanaka and Chandel, 2009). Under normoxic conditions, HIF-1α subunits are hydoxylated on prolines by prolyl hydroxylases (PHDs) (Hägg and Wennström, 2005; Hirsilä et al., 2003). Hydroxylated HIF-1α is recognized by the von Hippel-Lindau (pVHL) tumor suppressor leading to the ubiquitination and degradation of HIF-1α. During hypoxia, mROS inhibits the activity of PHDs allowing for the stabilization of HIF-1α subunits and HIF-mediated transcription (Hamanaka and Chandel, 2009). Thus, hypoxia-induced mROS can be viewed as a double-edged sword by inducing mitochondrial damage and activating mitophagy pathways to remove damaged mitochondria. Under persistent hypoxic conditions, mROS levels could remain elevated and the overall content of mitochondria would be decreased by activated mitophagy resulting in insufficient ATP production for cell proliferation. Low mitochondrial content has been observed in solid tumors, which contain large regions associated with a low oxygen concentration, including hepatocellular carcinoma, renal cell carcinoma, and ovarian cancer (Cuezva et al., 2002; Simonnet et al., 2002; Wang et al., 2006).

In fact, most cancer cells do not rely primarily on mitochondrial oxidative phosphorylation to generate the energy required for cellular processes (Fantin et al., 2006; Moreno-Sánchez et al., 2007), but on aerobic glycolysis, which is known as “the Warburg effect” (Hsu and Sabatini, 2008; Vander Heiden et al., 2009). Aerobic glycolysis is a glycolytic process that occurs even in the presence of oxygen. HIF-1 mediates the metabolic adaptation by coordinately regulating genes encoding glycolytic enzymes (Semenza, 2011; Semenza et al., 1996; Seagroves et al., 2001), and activating expression of both pyruvate dehydrogenase kinase 1 (PDK1) and lactate dehydrogenase A (LDHA) (Kim et al., 2006; Papandreou et al., 2006; Stubbs and Griffiths, 2010; Semenza, 2007).

It is estimated that 15–20% of human cancers are associated with infection by oncogenic viruses (D’Agostino and Bernardi, 2005; McLaughlin-Drubin and Munger, 2008; Dayaram and Marriott, 2008). A key step in viral tumorigenesis is the specific interaction of a virus oncogenic gene product(s) with mitochondria (Chatterjee et al., 2011; Kroemer, 2006). An

emerging body of evidence has demonstrated that diverse viruses target mitochondria as a mechanism to alter cell physiology, including cell survival (Ohta and Nishiyama, 2011; Galluzzi et al., 2008). Also, some oncogenic viruses can generate ROS via their oncogenic products: for example, hepatitis B virus (HBV) X protein (HBx); hepatitis C virus (HCV) core, E1 and NS3; human papillomavirus 18 (HPV-18) E2; human T-cell leukemia virus 1 (HTLV-1) p13 and Tax (Fig. 1). It is generally believed that virus infection-induced ROS triggers oxidative DNA damage, which can lead to cancer (Demple and Harrison, 1994; Lu et al., 2001; Dizdaroglu, 1992). However, other aspects of ROS-related physiology and pathology have not been extensively studied in viral oncogenesis. Furthermore, ROS-producing virus oncogene products play an essential role in virus replication, which may require high metabolic activity of host cells in addition to robust cell proliferation. Thus, it is likely that oncogenic viruses hijack mitochondria quality control and metabolic adaptation pathways to promote virus replication. This review will highlight recent progress on oncogenic viruses and their functional interactions with mitochondria that promote viral oncogenesis.

Hepatitis B virus (HBV)

More than 350 million people worldwide are chronically infected with HBV. The chronic infection is associated with the development of severe liver diseases including hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). HBV is a DNA virus belonging to the *Hepadnaviridae* family and has a highly compact genome of about 3200 bases in length. This genome contains four overlapping open reading frames that encode the viral core protein, surface proteins, reverse transcriptase and nonstructural X protein (HBx) (Koike, 2009). HBx is a multifunctional protein that regulates cellular signaling, transcription, proliferation, DNA repair, apoptosis and protein-degradation pathways. These activities may contribute not only to HBV replication but also to the development of HCC. One controversial aspect regarding HBx is whether this protein is anti-apoptotic or pro-apoptotic (Rawat et al., 2012).

HBx is predominantly located in the nucleus of HBV-infected hepatocytes at low expression levels, whereas at high expression levels it is mostly cytoplasmic. A portion of cytoplasmic HBx localizes to the mitochondrial outer membrane (Fig. 2) (Henkler et al., 2001; Huh and Siddiqui, 2002; Li et al., 2008). Interestingly, HBx is not observed in mitochondria at lower expression levels (Henkler et al., 2001). Mitochondrial localization of HBx triggers excessive mROS production, possibly by altering the expression of proteins involved in the oxidative phosphorylation pathway (Lee et al., 2004; Jung and Kim, 2013; Koike, 2009). HBx-induced mROS have been shown to be both pro-apoptotic and anti-apoptotic (Rawat et al., 2012). Excess mROS can induce apoptosis by mitochondrial membrane depolarization through modulation of the mitochondrial permeability transition pore (MTPC) (Shirakata and Koike, 2003). However, in primary hepatocytes, HBx regulation of the MPTC varies depending on the status of NF-κB activation. HBx activation of NF-κB suppressed mitochondrial membrane depolarization; however, when NF-κB signaling was blocked, HBx induced the MPTC (Clippinger and Bouchard, 2008). It is noteworthy that ROS can activate NF-κB (Li et al., 1998). Furthermore, recent studies demonstrate that HBx-induced ROS promotes HCC via dysregulation of the PTEN/Akt pathway (Ha, 2010), and HBx

phosphorylation at serine 31 by Akt is essential for the anti-apoptotic activity of HBx (Lee et al., 2012b), indicating that cellular signaling events initiated by HBx-induced ROS accumulation could enhance cell survival and induce the development of HCC. Taken together, these results suggest that ROS levels or the availability of ROS-activated NF-κB or Akt, depending on the cellular context, may determine whether HBx is pro-apoptotic or anti-apoptotic.

However, there is no direct evidence that HBx-induced ROS is involved in HIF-1 activation or stabilization. Previous studies showed that HIF-1α was stabilized by direct HBx binding to the bHLH/PAS domain of HIF-1α, thereby preventing degradation of HIF-1α (Yoo and Lee, 2004; Yoo et al., 2003). HIF-1α was also up-regulated by HBx-stimulated transactivation through metastasis-associated protein 1 (MTA1), histone deacetylase 1 (HDAC1) and the mitogen-activated protein kinase pathway (Yoo et al., 2008). Furthermore, a recent study demonstrated that C-terminal mutations of HBx could regulate the ability of HBx to induce HIF-1α (Liu et al., 2014). Considering that the C-terminal region of HBx is involved in mitochondrial localization and oxidative stress (Jung and Kim, 2013; Huh and Siddiqui, 2002; Li et al., 2008), it is likely that mROS may mediate HBx activation of HIF-1α, possibly resulting in metabolic adaptation and activation of mitophagy.

HBx has recently been shown to utilize autophagy pathways for cell survival. Yi Mao *et al* reported that starvation-induced cell death was greatly increased in HBX-expressing hepatic and hepatoma cell lines treated with the autophagy inhibitor 3-methyladenine or transfected with an siRNA specific for the autophagy regulatory gene, beclin 1, indicating that HBx-induced autophagy was essential for cell survival (Mao et al., 2011). HBx can promote autophagy through the PI3K/Akt pathway (Wang et al., 2013a) and activates the autophagic lysosomal pathway in HepG2 cells via up-regulation of LC3-II, LC3-I, beclin 1 and lamp2a proteins (Wang et al., 2013b). Consistent with HBx activation of autophagy, HBx may also trigger mitophagy since it induced mitochondrial clustering in the perinuclear region (Kim et al., 2007). Indeed, HBV infection or HBx expression promoted the mitochondrial translocation of the dynamin-related protein (Drp1) by stimulating its phosphorylation at Ser616, thus leading to mitochondrial fission (Fig. 2) (Kim et al., 2013a). These events were also associated with increased gene expression of Parkin, PINK1 and LC3B and Parkin recruitment to the mitochondria, culminating in mitophagy (Kim et al., 2013a). These results suggest that HBV activates the mitophagy pathway via HBx protein to suppress virus-induced apoptosis. However, it remains unclear how HBx-induced ROS and HIF-1 activation are related to mitochondrial quality control.

It is well established that HBx plays a crucial role in HBV replication through several mechanisms (refer to recent review papers (Rawat et al., 2012; Feitelson et al., 2014)). However, it has not been elucidated how HBx-induced ROS and associated mitochondrial activities including metabolic adaptation, apoptosis and mitophagy contribute to HBV replication. A tight regulation of HBx-induced ROS is likely essential for efficient HBV replication, and chronic liver diseases and HCC.

Hepatitis C virus (HCV)

There are approximately 200 million people worldwide infected with HCV (Mohd Hanafiah et al., 2013; Gravitz, 2011), a chronic infection that frequently progresses to liver fibrosis and cirrhosis, various metabolic alterations (Adinolfi et al., 2011; Arrese et al., 2010) and the development of HCC or non-Hodgkin lymphoma (Jin, 2007; Hartridge-Lambert et al., 2012). HCV is an RNA virus belonging to the *Flaviviridae* family and has a genome of about 9600 bases long, consisting of a long open reading frame encoding a polyprotein precursor of 3010 amino acids (Kato, 2000). The HCV polyprotein is cleaved by cellular and viral proteases into ten different products, consisting of structural (core, E1 and E2) and nonstructural proteins (NS1, NS2, NS3, NS4A, NS4B, NS5A and NS5B) (Ashfaq et al., 2011).

A remarkable feature of HCV-associated pathogenesis is the ROS production in HCV-infected cells (refer to recent review papers for detail (Ivanov et al., 2013; Paracha et al., 2013)). In contrast to HBV, HCV encodes several ROS-producing proteins: core, E1, E2, NS3/4A, NS4B and NS5A. Among them, core is a potent ROS inducer and induces oxidative stress on par with that observed during chronic HCV infection (Korenaga et al., 2005; Okuda et al., 2002; Schwer et al., 2004; Paracha et al., 2013). HCV core enhances ROS production, mainly in mitochondria, by inhibiting oxidative phosphorylation complex I (Korenaga et al., 2005) and by stimulation of calcium uniporter activity (Fig. 3) (Li et al., 2007). Also, HCV core induces mitochondrial dysfunction by enhancing the expression of prohibitin, a chaperone of mitochondrial respiratory enzymes (Tsutsumi et al., 2009). HCV core is localized in mitochondria, and in mitochondria-associated membranes (MAM) where it elevates mitochondrial calcium concentration, which in turn is involved in MPTP opening, mitochondrial depolarization and subsequent mitochondrial damage (Benali-Furet et al., 2005). This oxidative stress triggers DNA damage and lipid peroxidation in HCV-infected cells (Machida et al., 2006).

HCV has evolved several strategies including metabolic adaptation and mitophagy in response to oxidative stress. Although there is little evidence that HCV core activates HIF-1α (Liu et al., 2011), HCV infection leads to stabilization of HIF-1α through oxidative stress (Nasimuzzaman et al., 2007; Ripoli et al., 2010). HIF-1α stabilization requires the activation of NF-κB, STAT3, PI3K/AkT and p42/44 mitogen-activated protein kinase (Fig. 3), suggesting that HCV infection or HCV core-induced ROS may be involved in the activation of these signaling pathways akin to HBx activation of NF-κB and PI3K/Akt (Machida et al., 2006; Paracha et al., 2013). The HIF-1α protein promotes glycolytic adaptation in Huh-7.5 cells harboring infectious HCV (Ripoli et al., 2010) as well as HCV replication and metastasis properties of HCC by up-regulation of vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β) (Wilson et al., 2012).

Moreover, it is likely that HCV-induced mitochondrial dysfunction leads to mitophagy. Indeed, HCV infection promotes the formation of PINK1/Parkin-mediated mitophagy by up-regulating the expression of PINK1 and Parkin (Kim et al., 2013c). Also, this same study demonstrated that HCV replication was diminished when PINK1 and Parkin were depleted, indicating that mitophagy was essential for HCV replication. However, there is currently no

direct evidence that HCV core-induced mitochondrial dysfunction activates mitophagy. Because HCV core was recently reported to activate autophagy by up-regulating LC3B and Atg5 through ER stress-induced signaling (Wang et al., 2014), it is likely that HCV core is involved in the mitophagy pathway to remove damaged mitochondria.

Human papillomavirus (HPV)

HPVs have a DNA genome and are classified into two groups based on pathogenicity: low-risk and high-risk. At least 15 high-risk HPVs (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) are linked to the development of several types of cancers, including cervical and oropharyngeal carcinomas (Gabriela et al., 2013; Ramqvist and Dalianis, 2010; Madkan et al., 2007). The genome of HPV consists of 8,000 bases and can be subdivided into three major regions: early, late and a long control region. The early region encodes six nonstructural regulatory proteins (E1, E2, E4, E5, E6 and E7) (Danos et al., 1982). E1 and E2 are involved in viral DNA replication and the regulation of early transcription. E4 is expressed during productive infection and associates with cytokeratin collapse. E5, E6 and E7 are viral oncogenes that are capable of cell immortalization and transformation. E6 and E7 inactivate two key tumor suppressor proteins p53 and pRb, respectively (Mu and Howley, 2002). Thus far, however, it is unclear whether E6 and E7 regulate redox regulation or mitochondrial metabolism in the development of cancer. Recently, HPV-16 E6 and E7 were shown to inhibit apoptosis by down-regulating the expression of the C1q receptor (gC1qR/p32/C1QBP/HABP1) (Gao et al., 2011), a mitochondrial surface protein overexpressed in certain cancers. Because down-regulation of gC1qR in human cancer cells strongly shifts metabolism from oxidative phosphorylation to glycolysis (Fogal et al., 2010), it is likely that E6 and E7 regulate metabolic balance between oxidative phosphorylation and aerobic glycolysis, probably in the absence of severe mitochondrial dysfunction (Fig. 4).

Historically, E2 was classified as a viral “anti-oncogene” because E2 can repress the transcription of E6 and E7 in the context of HPV (Soeda et al., 2006; Bernard et al., 1989; Francis et al., 2000). However, recent data challenge this notion and unambiguously indicate that E2 proteins from high-risk HPVs (HPV-16 and HPV-18) actually exhibit oncogenic characteristics in cervical cancer progression (Bellanger et al., 2011). For example, these E2 proteins induce abnormal mitosis and chromosomal instability, together with DNA breaks during anaphase. Furthermore, E2 down-regulates anti-sense mitochondrial non-coding RNAs (ASncmtRNAs) (Villota et al., 2012), which are down-regulated in cancer cells (Burzio et al., 2009). Most E2 proteins are predominantly retained in the nuclei of infected cells, but HPV-18 and 16 E2s can shuttle between the nucleus and cytoplasm. A mass spectrometry study revealed that HPV-18 E2 associates with inner mitochondrial membrane proteins including components of the respiratory chain (e.g. complex III proteins) (Lai et al., 2013). Furthermore, electron microscopy analysis revealed that HPV-18 E2 localizes to mitochondria and modifies the cristae morphology of mitochondria (Lai et al., 2013). This study also demonstrated that E2-induced mitochondrial ROS correlates with stabilization of HIF-1α and increased glycolysis by up-regulation of the HIF target glycolytic genes PDK1 and carbonic anhydrase IX (CAIX) (Fig. 4). These mitochondrial functions were not observed with the non-oncogenic (low-risk) HPV-E2 protein, suggesting that modification

of cellular metabolism by high-risk HPV E2 proteins could play a role in the development of cancer by inducing metabolic adaptation.

On the other hand, little is known about whether high-risk E2 protein-induced ROS is involved in the initiation of mitophagy. Since HPV-18 E2-induced ROS did not induce apoptosis (Lai et al., 2013), the level of high-risk E2 protein-induced ROS may not be sufficient to induce mitochondrial damage.

Human T-cell leukemia virus type 1 (HTLV-1)

HTLV-1 is a complex delta-retrovirus that infects approximately 20 million people worldwide and is associated with an inflammatory neurological disease (HTLV-1-associated myelopathy/tropical spastic paraparesis [HAM/TSP]) and an aggressive T-cell leukemia (adult T-cell leukemia [ATL]). The HTLV-1 genome is flanked by long terminal repeats (LTRs) and contains *Gag*, *Pol* and *Env* genes that encode essential structural and enzymatic proteins typical of all retroviruses. In addition, the pX region encodes four open reading frames (ORF I, II, III and IV) that give rise to several regulatory and accessory proteins that influence viral replication, cell proliferation, survival and transformation. ORF I encodes the p12 accessory protein which contributes to cell proliferation and immune evasion by activation of JAK/STAT and NFAT pathways and downregulation of MHC class I proteins respectively (Bai and Nicot, 2012). ORF II yields p13 which can localize to either the nucleus or mitochondria and regulates cell proliferation and survival (Silic-Benussi et al., 2010b). ORF II also encodes p30, a nuclear protein that negatively regulates viral gene expression post-transcriptionally by retaining *tax/rex* mRNA in the nucleus (Nicot et al., 2004). p30 also regulates the cell cycle and the DNA damage response and is important for viral persistence *in vivo* (Anupam et al., 2013). ORF III encodes Rex which binds to the Rex response element on unspliced and singly spliced viral RNAs and shuttles these RNAs from the nucleus to the cytoplasm for translation by the host machinery (Bai et al., 2012). Tax is encoded by ORF IV and is essential for transactivation of viral gene expression by recruiting host transcription factors CREB and AP-1 and coactivators CBP/p300 to the LTR (Harrod et al., 1998). Tax is also a potent oncogene that drives cell transformation by inactivating tumor suppressors, modulating the cell cycle and constitutively activating pro-proliferative and anti-apoptotic signaling pathways such as NF-κB (Matsuoka and Jeang, 2007). Finally, the antisense strand of HTLV-1 encodes spliced and unspliced forms of HTLV-1 basic leucine zipper factor (HBZ). HBZ promotes T-cell proliferation and antagonizes Tax activation of viral transcription and NF-κB to establish viral latency (Zhao and Matsuoka, 2012).

Of the HTLV-1 accessory and regulatory proteins, both p13 and Tax have been shown to induce ROS (Fig. 5). p13 contains an amphipathic alpha helix domain between amino acids 20–35 important for targeting p13 to the mitochondria where it inserts into the inner mitochondrial membrane and induces an inward K+ current that increases ROS production and promotes apoptosis (Silic-Benussi et al., 2010c, 2009; Biasiotto et al., 2010; Silic-Benussi et al., 2010a). p13 does not appear to be sufficient to induce cell death, but rather sensitizes cells to pro-apoptotic stimuli such as Fas ligand (Saggioro et al., 2009). Tax also induces ROS production, possibly through contributions from CREB and NF-κB, which

correlates with DNA damage and cellular senescence (Kinjo et al., 2010). Tax may also induce ROS through interactions with ubiquitin-specific protease 10 (USP10), a component of stress granules (SGs) that plays critical roles in several SG-mediated activities, including inhibition of ROS production and ROS-dependent apoptosis (Takahashi et al., 2013). Tax inhibits arsenic-induced SG formation, stimulates ROS and enhances ROS-dependent apoptosis in T cells (Takahashi et al., 2013). Interestingly, cross-regulation between Tax and p13 has been reported that may impinge on production of ROS and cell survival (Silic-Benussi et al., 2010a). However, at this time the cellular source of Tax-induced ROS is unknown and requires further investigation.

Recent mass spectrometry experiments from our lab showed that Tax may interact with several mitochondrial proteins including Hsp60, methylcrotonoyl-coenzyme A carboxylase subunit alpha, mitochondrial import inner membrane translocase subunit TIM50, mitochondrial phosphate carrier protein isoform B and propionyl-coenzyme A carboxylase alpha chain (Gao and Harhaj, 2013). Furthermore, using biochemical fractionation assays and confocal microscopy, we have found that a significant fraction of Tax localizes to mitochondria (submitted for publication). Whether Tax indeed interacts with these mitochondrial proteins to regulate ROS and/or cell death is an important topic for future investigation.

Herpesviruses

Human herpesviruses constitute a family of nine DNA viruses: Herpes simplex virus-1 (HSV-1/HHV-1), Herpes simplex virus-2 (HSV-2/HHV-2), Varicella zoster virus (VSV/HHV-3), Epstein-Barr virus (EBV/HHV-4), Cytomegalovirus (CMV/HHV-5), HHV-6A, HHV-6B, HHV-7 and Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8). Among them, only EBV and KSHV are oncogenic and frequently found to cause cancers in aged and immunosuppressed individuals. EBV infection is linked to the development of endemic Burkitt's lymphoma, nasopharyngeal carcinoma, a subset of Hodgkin's disease and other malignancies of lymphoid and epithelial cell origin (Young and Rickinson, 2004). The proteins encoded by EBV latency genes, including six EBV-encoded nuclear antigens (EBNA-1, -2, -3A, -3B, -3C, and -5) and three latent membrane proteins (LMP-1, -2A, and -2B), induce cell transformation by activating multiple signaling pathways that regulate proliferation and apoptosis. However, there is no direct evidence that EBV-encoded proteins induce mROS production. Rather, EBNA-1 promotes genomic instability via production of ROS by transcriptionally activating the leukocyte NADPH oxidase NOX2 (Gruhne et al., 2009). In addition, LMP-1 expression in the nasopharyngeal carcinoma cell line Ad-AH promotes HIF-1α accumulation by activation of the p42/p44 MAPK pathway through ROS production, particularly H_2O_2 (Cuninghame et al., 2014).

KSHV is the etiological agent of several neoplasms including Kaposi's sarcoma, endothelial cell disease, and B cell malignancies primary effusion lymphoma and multicentric Castleman's disease (Ganem, 2006; Carbone and Gloghini, 2008). Similar to EBV, it is unknown if KSHV gene products induce mROS. Instead, the KSHV early lytic gene viral G protein-coupled receptor (vGPCR) triggers ROS production in mECK36 cells via a Rac1-NADPH oxidase pathway (Ma et al., 2013). Thus, it remains to be determined whether EBV

and KSHV infections induce mROS production and if so which viral gene products are responsible for mROS production.

CMV is a β-herpesvirus, with about 60–90% of adults having been infected by CMV at some time. CMV infections are usually asymptomatic but can be life-threatening for immunocompromised individuals such as HIV-1 infected patients and organ transplant recipients. Congenital CMV infection is also a major cause of morbidity in newly born infants and can lead to permanent disabilities. Thus far, CMV infection has not been clearly linked to the development of any human cancers, however CMV antigens have been detected in a large fraction of glioblastoma multiforme brain tumors. Whether CMV and its gene products regulate mROS production is currently unknown.

Conclusions

Several oncogenic viral gene products are known to induce oxidative stress in infected host cells or transfected cells. The best-known gene products are HBV HBx, HCV core, HPV E2 and HTLV-1 Tax (Table 1). These viral proteins generate ROS mainly in the mitochondria although it is unknown if HTLV-1 Tax can produce ROS in mitochondria. ROS have been recognized as a major player in the development of carcinoma, in particular, by inducing oxidative DNA damage that leads to oncogenic mutations. Generally, ROS induces cell death when produced in excessive amounts. Cells have established several strategies to survive in response to the deleterious effect of ROS: anti-apoptosis, autophagy and metabolic adaptation, resulting in malignancy along with genetic alterations. Similarly, ROS-producing oncogenic viral gene products hijack the survival mechanisms of host cells and together with ROS-induced genetic changes promote cellular transformation or viral replication. In this review, we focused on oncogenic viral regulation of mitophagy and metabolic adaptation by which mROS levels could be down-regulated. However, it remains largely unknown how oncogenic viruses precisely regulate mitophagy and metabolic adaptation pathways for oncogenesis or viral replication. In particular, little is known about the exact mechanisms underlying mitophagy pathways. On the other hand, EBV was shown to induce structural alterations of mitochondria after infection or expression of its gene products (LaJeunesse et al., 2005; Pal et al., 2014), but it is unknown whether EBV or EBV gene products induce mROS and mitophagy. Recently, Merkel cell polyomavirus (MCV) was identified as the causal agent for Merkel cell carcinoma, a rare skin cancer (Feng et al., 2008), but there is no evidence that MCV and its oncogenic gene product T antigen are involved in mROS production. Therefore, it would be of great interest to examine whether the oncogenic viruses EBV, KSHV and MCV regulate mROS-related mitochondrial physiology and metabolic adaptation during lytic productive replication and oncogenesis.

Acknowledgments

The laboratories of E.W.H and Y.B.C. are funded by National Institutes of Health grants RO1CA135362 and R21AI103379 respectively.

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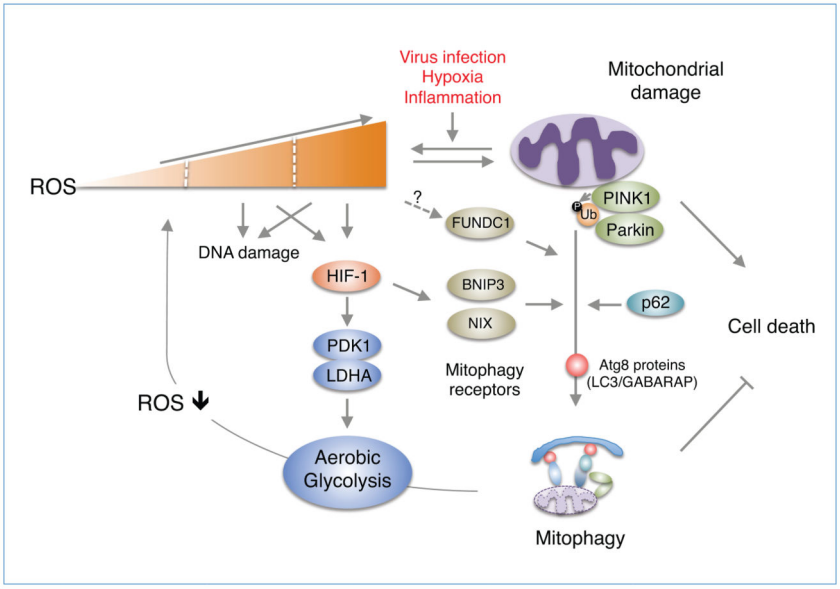

Figure 1. Regulation of ROS homeostasis through mitophagy and metabolic adaptation

Mitochondrial ROS induced by virus infection can lead to mitochondrial dysfunction or damage. Accumulation of damaged mitochondria generates excessive mROS, which promotes oxidative stress, DNA damage and cell death. To mitigate the harmful effects of mROS and reduce mROS levels, cells induce mitophagy, by which damaged mitochondria are cleared, via the PINK1/Parkin complex (Youle and Narendra, 2011; Novak, 2012) and presumably HIF-1 activation of mitophagy receptors NIX and BINP3 or FUNDC1 (Ding and Yin, 2012). PINK1 phosphorylates ubiquitin (Ub) to activate Parkin (Kane et al., 2014; Shiba-Fukushima et al., 2012), which in turn induces the ubiquitination of mitochondrial proteins. The p62/SQSTM1 adaptor links the ubiquitinated mitochondria to the Atg8 family proteins (LC3/GABARAP) essential for the autophagosome maturation. Also, HIF-1 promotes metabolic adaptation (aerobic glycolysis) via the activation of PDK1 and LDHA (Kim et al., 2006; Cuninghame et al., 2014) to bypass mitochondrial oxidative phosphorylation generating mROS or presumably generate ATP in cells actively undergoing mitophagy or containing a few mitochondria.

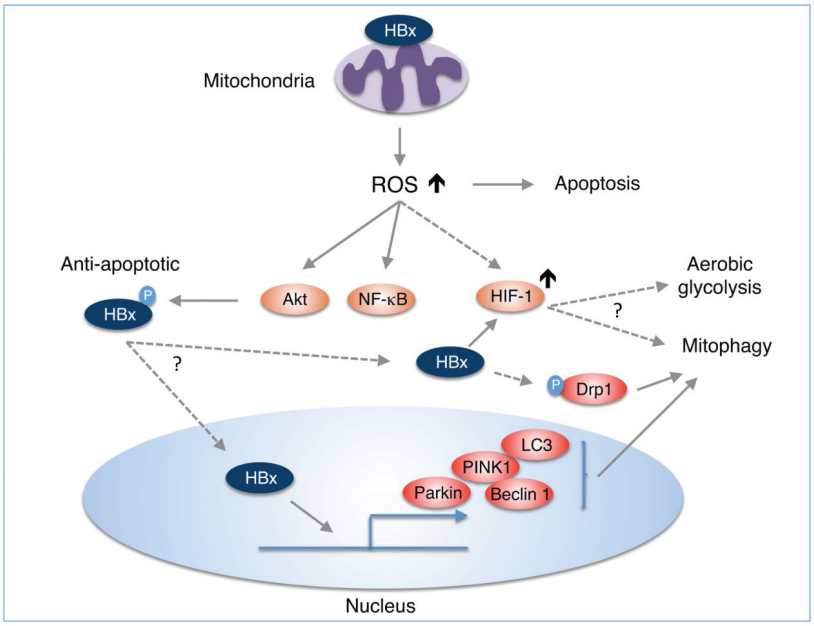

Figure 2. Possible role of HBV HBx-induced mROS in mitophagy and metabolic adaptation

HBV infection induces the production of mROS via its gene product HBx and regulates mitophagy. Anti-apoptotic role of HBx may be dependent on the ability of HBx to eliminate damaged mitochondria via mitophagy. HBx, presumably the anti-apoptotic form phosphorylated by Akt (Lee et al., 2012b), can upregulate the expression of mitophagic proteins including PINK1, Parkin, Beclin, LC3 and also induce the phosphorylation of Drp1 to promote mitophagy (Kim et al., 2013b). However, the functional significance of HBx activation of HIF-1 is largely unknown.

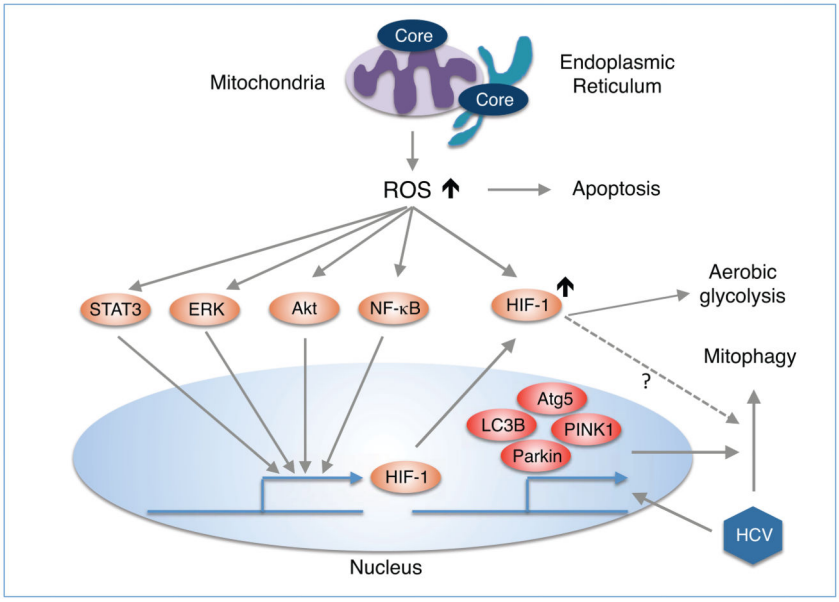

Figure 3. Possible role of HCV core-induced mROS in mitophagy and metabolic adaptation

HCV infection induces the production of mROS mainly via its gene product core, and regulates mitophagy through the upregulation of PINK1 and Parkin (Kim et al., 2013c). However, there is no direct evidence that HCV core regulates mitophagy although it upregulates LC3B and Atg5 through ER-stress-induced signaling (Wang et al., 2014). HCV core activates and stabilizes HIF-1 by ROS or several cellular signaling pathways such as NF-κB, STAT3, Akt and Erk and then promotes metabolic adaptation (Ivanov et al., 2013).

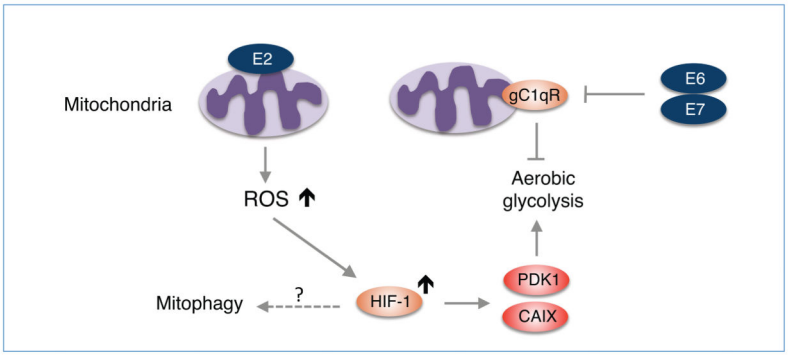

Figure 4. HPV-18 E2 regulates ROS production

High-risk HPV-18 E2 localizes to mitochondria and induces ROS that stabilizes HIF-1, which in turn activates PDK1 and CAIX enzymes to promote aerobic glycolysis (Lai et al., 2013). HPV can also promote aerobic glycolysis by inhibition of gC1qR through E6 and E7 (Gao et al., 2011). There is no evidence that HPV infection and its gene products including E2, E6, and E7 induce mitophagy.

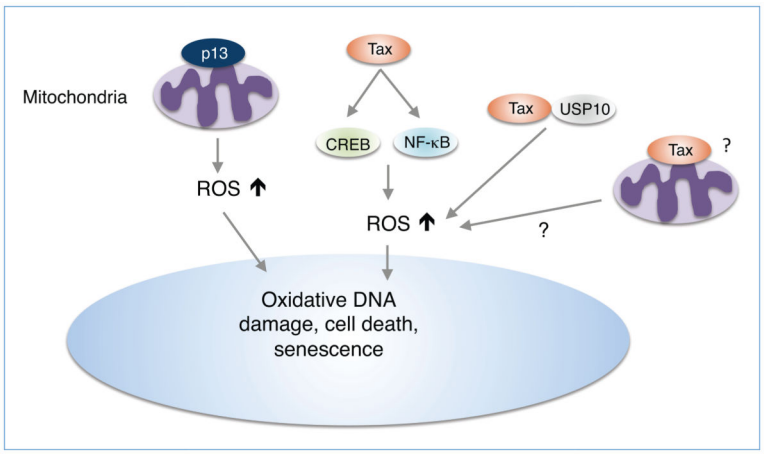

Figure 5. HTLV-1 p13 and Tax proteins regulate ROS production

HTLV-1 p13 localizes in the mitochondria and induces an inward K+ current that triggers mitochondrial depolarization, an increase in respiratory chain activation and ROS production (Silic-Benussi et al., 2009; Biasiotto et al., 2010). HTLV-1 Tax increases ROS production via CREB and NF-κB activation, interaction with USP10 (Takahashi et al., 2013) and/or localization in mitochondria. Increased ROS by p13 and Tax results in increased DNA damage, senescence and possibly cell death.

Table 1

Oncogenic viral gene products triggering the production of mitochondrial reactive oxygen species.

Virus	Viral protein	Mechanism to induce mROS production	Reference
HBV	HBX	May alter the expression of proteins involved in oxidative phosphorylation.	Jung & Kim, 2013, Koike, 2009, Lee *et al*., 2004
HCV	Core	Inhibits oxidative phosphorylation complex I.	Korenaga *et al*., 2005
		Stimulates calcium uniporter activity.	Li *et al*, 2007
HPV	E2	Unknown	
HTLV-1	p13	Induces an inward potassium current at the mitochondrial inner membrane.	Silic-Benussi *et al*., 2009 Biasiotto *et al*., 2010
	Tax	Unknown	