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Endoplasmic reticulum & mitochondrial calcium homeostasis: The interplay with viruses

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Abstract

Calcium ions (Ca^{2+}) act as secondary messengers in a plethora of cellular processes and play crucial role in cellular organelle function and homeostasis. The average resting concentration of Ca^{2+} is nearly 100 nM and in certain cells it can reach up to 1 μM. The high range of Ca^{2+} concentration across the plasma membrane and intracellular Ca^{2+} stores demands a well-coordinated maintenance of free Ca^{2+} via influx, efflux, buffering and storage. Endoplasmic Reticulum (ER) and Mitochondria depend on Ca^{2+} for their function and also serve as major players in intracellular Ca^{2+} homeostasis. The ER-mitochondria interplay helps in orchestrating cellular calcium homeostasis to avoid any detrimental effect resulting from Ca^{2+} overload or depletion. Since Ca^{2+} plays a central role in many biological processes it is an essential component of the virus-host interactions. The large gradient across membranes enable the viruses to easily modulate this buffered environment to meet their needs. Viruses exploit Ca^{2+} signaling to establish productive infection and evade the host immune defense. In this review we will detail the interplay between the viruses and cellular & ER-mitochondrial calcium signaling and the significance of these events on viral life cycle and disease pathogenesis.

Keywords

Virus; Calcium; Mitochondria; Mitochondrial calcium uniporter; Calcium homeostasis; Antiviral signaling

1 Introduction

The ubiquitous role of calcium ions (Ca^{2+}) as a secondary messenger in a plethora of cellular processes is well known. This simple bivalent cation regulates complex signaling

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mechanisms and acts as a torch-bearer of many extracellular and intracellular signaling pathways (Contreras et al., 2010; Song et al., 2019; Wang et al., 2015). There is a huge variability in Ca^{2+} concentration across different subcellular compartments; for instance Ca^{2+} concentration in the intracellular stores like Endoplasmic Reticulum (ER) and Golgi apparatus is around 200–650 μM, whereas in the cytosol the Ca^{2+} concentration is around 100 nM under resting conditions (Berridge et al., 2000; Raffaello et al., 2016; Zampese and Pizzo, 2012). Ca^{2+} concentration in the extracellular matrix is also several fold high (1–2 mM) compared to intracellular concentrations. At times the cytosolic Ca^{2+} concentration sharply increases to 1–3 μM due to certain cellular events like Ca^{2+} release from intracellular stores, or rapid influx from extracellular milieu. The ER and Golgi help in maintaining cellular Ca^{2+} homeostasis by acting as cellular Ca^{2+} stores. Whereas, the mitochondria functions as a Ca^{2+} buffering organelle and plays a vital role in cellular Ca^{2+} homeostasis by transiently taking up high levels of Ca^{2+} directly from cytosol or intracellular stores during conditions involving sharp rise in cellular Ca^{2+} concentration.

Overall the cellular Ca^{2+} homeostasis is met by well-coordinated processes of calcium influx, efflux, buffering and storage (Tang et al., 2015). Organelles like ER and mitochondria are an integral part of these processes and are vital to prevent detrimental effects resulting from large Ca^{2+} gradient flux across the membranes (Wang et al., 2015).

2 Calcium and Mitochondria: The intricate connection

Mitochondria, are highly dynamic double-membrane organelles with pleiotropic functions and serve as a hub of many signaling events (Paupe and Prudent, 2018; Romero-Garcia and Prado-Garcia, 2019). Mitochondria act as transient calcium buffers and can accommodate a broad range of intracellular calcium (50–500 nM) (Romero-Garcia and Prado-Garcia, 2019). While many cellular and mitochondrial functions rely on Ca^{2+}, in turn mitochondria serve a vital role in modulating cellular Ca^{2+} dynamics, hence both share a symbiotic association. Deregulation or disruption of either of their functions may lead to disruption in cellular homeostasis and lead to cell death (Bravo-Sagua et al., 2017). For instance, a recent study in rat ventricular myocytes suggest that enhanced cytosolic Ca^{2+} can promote mitochondrial fragmentation or fission. On the other hand, depletion of cytosolic Ca^{2+} promotes the active movement of mitochondria towards cellular Ca^{2+} stores like ER and promotes the formation of ER-mitochondrial contacts through mitochondrial associated membranes (MAMs) and uptake of mitochondrial Ca^{2+}. Interestingly, mitochondrial fragmentation will aide/faciitate efficient transport of mitochondria (Bravo-Sagua et al., 2017; Hom et al., 2010). Ca^{2+} uptake by mitochondria is also affected by the mitochondrial size, morphology and vicinity of mitochondria from the Ca^{2+} release sites. For instance, the tubular interconnected mitochondrial network has a higher Ca^{2+} uptake capacity due to a bigger matrix volume (Bravo-Sagua et al., 2017).

Ca^{2+} plays specific roles in distinct mitochondrial compartments. Ca^{2+} in the intermembrane space (IMS) regulates the functions of many inner mitochondrial membrane (IMM) resident enzymes. Certain Ca^{2+} binding EF-hand containing substrate carrier proteins are also regulated by Ca^{2+}. Such substrate carriers can sense an increase in cytosolic Ca^{2+} level and accordingly pass metabolite and cofactors into the mitochondrial matrix to accelerate several

metabolic reactions. In the mitochondrial matrix, Ca^{2+} is required for ATP production via the TCA cycle and ETC (Denton, 2009). Ca^{2+} levels in the mitochondrial matrix also regulates cAMP activation through protein kinase A dependent pathway, which in turn regulates ATP production capacity of the mitochondria (Di Benedetto et al., 2013). Although Ca^{2+} is required for ATP production, excess influx of Ca^{2+} into mitochondrial matrix to support accelerated ATP production can lead to higher ROS production, which eventually induces loss of mitochondrial membrane potential (MMP). These processes in combination result in the opening of mitochondrial transition pore (mPTP) and release of apoptotic factors. The opening of mPTP can also be triggered by excess ROS, lower H^+ ions in the mitochondrial matrix and by direct interaction with polyphosphates (Stansfield, 2014). The crucial interconnections of Ca^{2+} and mitochondria are shown to be deregulated in many human diseases and are also exploited by invading pathogens for their benefit.

2.1 Mitochondrial calcium transport pathways

Though a moderate level of mitochondrial Ca^{2+} is beneficial in terms of cellular energy metabolism, mitochondria cannot resist higher Ca^{2+} levels for a prolonged period, which may lead to mitochondrial membrane collapse and cell death (Bravo-Sagua et al., 2017). Therefore, the Ca^{2+} influx and efflux across the mitochondrial membrane are tightly regulated through several ion channels, pumps and Ca^{2+} binding proteins (Zampese and Pizzo, 2012) (Fig. 1).

2.1.1 Mitochondrial Ca^{2+} uptake—To enter mitochondria, Ca^{2+} needs to travel through the ion-permeable outer mitochondrial membrane (OMM) followed by the ion impermeable inner mitochondrial membrane (IMM). The permeability of the OMM can be attributed to the voltage-dependent anion channel (VDAC). Earlier studies on IMM have mentioned that it carries out Ca^{2+} uptake in a rate-limiting manner mediated through electrochemical gradient generated through oxidative phosphorylation (Drago et al., 2011). However, the recent discovery of mitochondrial calcium uniporter (MCU) in 2011 has changed this notion. MCU is the major player involved in Ca^{2+} transport through IMM in a highly regulated manner (Baughman et al., 2011; De Stefani et al., 2011). Ca^{2+} uptake through MCU at a very high conductance rate happens through rapid uptake mode (RaM) in specialized cells like heart and liver cells even at sub-optimal cytosolic Ca^{2+} concentration (50–100 nM) (Gunter and Gunter, 2001; Sparagna et al., 1995). Surprisingly, MCU knockout mice show minimal alteration in mitochondrial bioenergetics despite great reduction in mitochondrial matrix Ca^{2+} levels. However, uptake of mitochondrial Ca^{2+} was not completely abolished in these mice suggestive of alternative Ca^{2+} uptake pathway that may help mitochondria adapt to adverse situations like these. The other channels involved in mitochondrial Ca^{2+} transport include ryanodine receptor 1 (mRyR1), Letm1 (leucine zipper-EF-hand containing transmembrane protein 1) and uncoupling protein 2 and 3 (UCP2 and 3) (Belosludtsev et al., 2019; Elustondo et al., 2017). mRyr1 is mostly found in metabolically active cells like cardiac cells and neurons owing to their higher conductance rate despite the high energy required by mRyr1 (Holmström et al., 2015). Letm1 is also known to play a role in Ca^{2+} efflux through H+ exchange and it is also known to act as a K^+/H^+ exchanger. However, there is a disagreement over its primary role as a Ca^{2+} or K^+ exchanger (Hashimi et al., 2013; Jiang et al., 2009; Li et al., 2019; Nowikovsky et al., 2007). UCP2 and 3 have

been recently implicated in mammalian Ca^{2+} transport as well as in the regulation of MCU in association with other cellular proteins (Trenker et al., 2007).

2.1.2 MCU: Key player in mitochondrial calcium transport—MCU, a product of the *ccdc109a* (chromosomal location: 10q22.1) gene is a recently discovered transmembrane protein that has gathered attention because of its key role in mitochondrial Ca^{2+} uptake. The function of MCU is coordinated by many regulatory proteins and the entire complex is termed as the MCU complex (Fig. 2). It consists of two outer subunits named mitochondrial calcium uptake 1 and 2 (MICU1 and MICU2), a ~ 10 kDa single-pass membrane protein EMRE and MCU regulator 1 (MCUR1). While MICU1 and MICU2 act as calcium sensors that enable selective ion transport and control Ca^{2+} influx (Baughman et al., 2011; Perocchi et al., 2010; Plovanich et al., 2013), EMRE serves as the middle man between components of the MCU complex and its regulators and allows Ca^{2+} access (Sancak et al., 2013; Tsai et al., 2017). MCUb is a dominant-negative regulator of MCU and shares 50% sequence similarity with MCU (Belosludtsev et al., 2019; Raffaello et al., 2013). Another regulator MCUR1 establishes a connection between MCU and EMRE and helps in MCU complex final assembly (Mallilankaraman et al., 2012; Tomar et al., 2016).

2.1.3 Mitochondrial Ca^{2+} efflux pathways—Mitochondrial Ca^{2+}efflux is equally important as its uptake to maintain intracellular Ca^{2+} homeostasis. Ca^{2+} efflux at the mitochondrial membrane is majorly coordinated by $Na^{+}/Ca^{2+}/Li^{+}$ exchanger NCLX (Khananshvili, 2013). This process is also coordinated by Letm1, (Shao et al., 2016), the transient opening of mPTP and lipid pores (Briston et al., 2019; Sultan and Sokolove, 2001). Other factors like high levels of ROS (by product of oxidative phosphorylation) can also lead to mPTP opening. Persistent opening of mPTP leads to release of proapoptotic factor from mitochondria and leads to apoptosis. This dysregulation of Ca^{2+} efflux from mitochondria has been implicated in human pathologies like muscular dystrophy and neurodegenerative disorders (Briston et al., 2019).

2.2 Mitochondria and ER intimacy: The MAM contacts

Cellular Ca^{2+} signaling occurs by dynamic crosstalk between ER and mitochondria. Ca^{2+} release from intracellular stores like ER or Ca^{2+} influx through plasma membrane modulates the mitochondrial redistribution and coupling between ER and mitochondria (Bravo et al., 2011). A Ca^{2+} rich microenvironment is created near the ER membrane that promotes the association of ER with mitochondria through MAMs. Around 20% of the mitochondrial surface remains in close contact with ER through the MAMs that are enriched with more than 1000 proteins (Gomez-Suaga et al., 2017). The important role of some of them is already discussed elaborately in many previous reviews (Belosludtsev et al., 2019; van Vliet et al., 2014). Transfer of Ca^{2+} between ER and mitochondria at these contact sites is regulated in a coordinated manner by the ER Ca^{2+} channels IP3R, mitochondrial outer membrane Ca^{2+} channel VDAC1 and the cytosolic chaperone Grp75 (Drago et al., 2011; Duchen, 1999; Poston et al., 2013). Loss in the MAMs architecture and its dysfunction has been implicated in neurodegenerative disorders and diabetes.

2.2.1 ER-Mitochondria Ca^{2+} crosstalk: Role in cellular bioenergetics/metabolism—

ER-mitochondrial Ca^{2+} transport is crucial for cellular metabolism (Rossi et al., 2019) and ER stress regulation. Ca^{2+} influx and accumulation in mitochondria regulate mitochondrial as well as cellular metabolism through activation of multiple mitochondrial enzymes and ETC components that in turn caters to the increased energy demand of ER-resident chaperones and protein folding enzymes during the management of ER stress (Bravo et al., 2011). RNA-dependent protein kinase (PKR) like ER kinase (PERK) is also a stress sensor in UPR that is abundantly present in MAM that helps propagation of Ca^{2+} and ROS from ER to mitochondria which in turn contributes to apoptosis (Verfaillie et al., 2012). Perturbance in ER-Mitochondria Ca^{2+} transfer also reduces the overall efficiency of TCA cycle leading to reduction in NADH and FADH2 levels, which leads to reduced OXPHOS capacity and ATP production. Low levels of cellular ATP can lead to induction of autophagy (Bootman et al., 2018). Hence, it is important to note that ER-mitochondrial Ca^{2+} signaling plays a major role not only in cellular bioenergetics but other cellular processes as well.

3 Viral infections and calcium signaling: A soft target or savior?

Calcium impacts many cellular processes hence is an important aspect of the virus-host interactions that govern the outcome of viral infections. Viruses can exploit this pivotal arm of cellular signaling to facilitate viral processes such as entry, replication, assembly and egress and to create an intracellular environment conducive to viral dissemination. Many viruses alter the cellular Ca^{2+} concentration in different compartments of the cell in a spatiotemporal manner, i) to activate Ca^{2+} dependent enzymes required to meet the high bioenergetic and metabolic demands, ii) to activate transcription factors required to support virus replication and iii) to regulate the innate immune response. The huge Ca^{2+} concentration gradient maintained across various cellular compartments and high tolerance of the host cell to subtle changes in Ca^{2+} level allows the viruses to effectively modulate cellular calcium signaling for their benefit without major detrimental effect on the host cells. However, the consequence of these spatiotemporal modulations of calcium concentration and signaling may lead to the onset of disease pathogenesis. In this section, we will address the interaction of the viruses with cellular calcium signaling and attempt to detail the significance of these events on the viral life cycle and disease pathogenesis (Fig. 3).

3.1 Human immunodeficiency virus (HIV)

HIV infection results in the depletion of functional CD4+ T cells leading to acquired immunodeficiency during infection. HIV infection of the permissive CD4+ T cells results in their death via apoptosis whereas the non-permissive bystander CD4+ T cells undergo death by activation of inflammasomes and pyroptosis (Doitsh and Greene, 2016). HIV Nef protein has been implicated in increase in levels of cytosolic Ca^{2+}. Nef acts as a master switch in the early HIV life cycle and has been associated with enhanced HIV pathogenicity. Distinct mechanisms are involved in Nef-mediated increase in intracellular Ca^{2+} in different cell lines. In Jurkat T cells, Nef expression promotes extracellular calcium influx while no release of calcium from ER stores is noticed despite Nef interaction with IP3R suggesting that enhanced physical coupling between IP3R and plasma membrane channels promote an increase in cytosolic Ca^{2+} (Berridge et al., 2000; Manninen and Saksela, 2002). Nef

expression in lymphoblastoid CEM cells resulted in the higher filling of non-ER calcium stores (Zegarra-Moran et al., 1999), whereas in pro-myelocytic HL60 differentiated cell lines it has resulted in decreased extracellular calcium influx. Moreover, an increase of non-ER calcium stores occurs via Nef interaction with Src-like protein tyrosine kinase through SH3 domain-mediated protein interaction (Foti et al., 1999). In agreement, agents that enhance cytosolic Ca^{2+} concentration promote HIV replication whereas agents that block the increase, inhibit HIV replication (Nye and Pinching, 1990; Papp and Byrn, 1995). HIV Nef-mediated release of ER Ca^{2+} results in activation of the nuclear factor of activated T cells (NFAT), which positively regulates HIV-1 replication and gene expression (Kinoshita et al., 1997). Nef expression is shown to induce transcriptional response imitating T cell receptor activation resulting in upregulation of HIV virulence mediators (Simmons et al., 2001). HIV viral protein R (Vpr), which mainly localizes to nucleus and mitochondria, induces the opening of mPTP by coordinating with Adenine Nucleotide Translocator (ANT) leading to the release of Ca^{2+} from mitochondria and subsequent apoptosis (Jacotot et al., 2001, 2000). Vpr interacts with and activates the Ca^{2+} responsive transcriptional coactivators like p300 and CREB-binding protein (CBP) (Kino et al., 2002). It co-operates with Nef in NFAT-dependent T cell activation favoring HIV transcriptional activation (Lahti et al., 2003). The HIV Tat (transactivator of transcription) is also shown to mediate Ca^{2+} deregulation. HIV Tat localizes to the nucleus and is an important regulator of viral gene expression and replication. HIV-infected cells release Tat into the extracellular milieu which may lead to disruption of Ca^{2+} signaling in bystander naive cells. HIV-associated dementia may be a consequence of neurotoxicity mediated by extracellular Tat protein. Tat has also been shown to increase cytosolic Ca^{2+} levels in a dose-dependent manner through the IP3R mediated release of ER Ca^{2+} pools in primary macrophages (Mayne et al., 2000). HIV gp120 which plays a crucial role in viral entry has also been implicated in dementia (Mattson et al., 2005). In human fetal astrocytes and neurons, HIV gp120 is shown to promote calcium influx through L-type calcium channels, Na+/H+ exchanger and NMDA-type excitatory amino acid receptor resulting in high intracellular Ca^{2+} levels (Holden et al., 1999) that subsequently promotes caspase-dependent neuronal apoptosis and HIV pathogenesis of dementia (Haughey and Mattson, 2002).

3.2 Hepatitis B virus (HBV)

HBV is a hepatotropic virus that causes chronic hepatitis eventually progressing into end-stage liver disease and hepatocellular carcinoma (HCC) (Shih et al., 2018). During HBV infection, the HBx protein interacts with VDAC and triggers the opening of the mPTP resulting in the release of mitochondrial Ca^{2+} to the cytoplasm. In parallel, the activation of Ca^{2+} ATPase transiently facilitates the uptake of Ca^{2+} by ER which is subsequently released back into the cytosol through the activation of IP3R (Xia et al., 2006). The elevated cytosolic Ca^{2+} promotes calcium-dependent activation of proline-rich tyrosine kinase 2 (Pyk2) and Focal Adhesion Kinase (FAK), which supports HBV reverse transcription and DNA replication (Bouchard et al., 2006, 2003, 2001). High cytosolic Ca^{2+} levels also induce NFAT dependent gene expression and are also implicated in the activation of JNK and MAPK signal transduction pathways (Lara-Pezzi et al., 1998; Oh et al., 2003). HBx mediated opening of mPTP also results in the release of cytochrome *c* from mitochondria which in turn activates caspase-3 that can further enhance cytosolic Ca^{2+} levels by cleavage

of the plasma membrane Ca^{2+} ATPase (PMCA) required for the efflux of cytosolic Ca^{2+} into the extracellular milieu (Chami et al., 2003). High levels of cytosolic Ca^{2+} also facilitates HBV core assembly (Choi et al., 2005). Overall, these studies demonstrate that HBx-induced Ca^{2+} signaling alterations not only promote HBV replication but also drive the onset of liver disease pathogenesis and progression into hepatocellular carcinoma.

3.3 Hepatitis C virus (HCV)

Like HBV, HCV is also a hepatotropic virus and is among the major etiological agents that cause chronic liver disease and HCC. HCV core and non-structural protein NS5A have been shown to modulate host calcium-signaling (Dionisio et al., 2009). HCV core and NS3/4A protease also localize to the outer mitochondrial membrane. HCV core protein promotes ER Ca^{2+} depletion by impairing SERCA pump function (Benali-Furet et al., 2005). The expression of HCV core fragment 37–191 is sufficient to upregulate ER oxidoreductin 1, triggers ER Ca^{2+} efflux and uptake by mitochondria via MCU (Ivanov et al., 2015). HCV may promote mitochondrial ATP production by facilitating mitochondrial Ca^{2+} uptake eventually leading to ROS production and apoptosis of HCV-infected cells (Li et al., 2007). The HCV viroporin protein p7 tends to form a hexameric channel on the ER membrane and may promote the release of ER Ca^{2+} to the cytosol. Molecules that block p7 have been effective in inhibiting viral replication (Griffin et al., 2003). HCV NS5A has also been implicated in ER Ca^{2+} efflux and uptake by mitochondria leading to elevated ROS levels and activation of NF-κB and STAT3, which supports cell growth and protects HCV-infected cells from apoptosis (Gong et al., 2001). A recent study suggests that treatment of primary monocyte-derived macrophages and THP-1 macrophages with HCV core protein induces a rapid increase of intracellular calcium through phospholipase C, which then leads to the activation of the NLRP3 inflammasome and IL-1β production (Negash et al., 2019). These detrimental effects of HCV viral proteins on calcium signaling pave way for the pathogenesis of the chronic liver disease and carcinogenesis associated with HCV infection.

3.4 Human T-lymphotropic Virus type-I (HTLV-1)

HTLV-1 infection is associated with adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) (Rajamani et al., 1995). $p13^{II}$ is an HTLV accessory protein that localizes to the inner mitochondrial membrane (IMM) (Ciminale et al., 1999) and is shown to promote mitochondria depolarization and swelling. $p13^{II}$ affects the mitochondrial Ca^{2+} retention and sensitizes the $p13^{II}$ expressing T lymphocytes to ceramide or Fas ligand-induced apoptosis (D'Agostino et al., 2005). Further study suggests that $p13^{II}$ reduces mitochondrial Ca^{2+} uptake by triggering inward K^+ current and inner membrane depolarization (Biasiotto et al., 2010). Another protein $p12^{I}$ encoded by the ORF I of HTLV-1 is enriched in the ER and *cis*-Golgi compartments where it binds to two ER-resident proteins calreticulin and calnexin which play a major role in ER calcium storage (Ding et al., 2001). $p12^{I}$ expression results in increased basal levels of cytoplasmic Ca^{2+} due to the release of ER Ca^{2+} by IP3R as well as by activation of Calcium Release-Activated Calcium (CRAC) channels in the plasma membrane. The increase in cytosolic Ca^{2+} levels promotes NFAT mediated transcriptional upregulation and facilitates proviral DNA integration and optimal infectivity of HTLV by activation of host cells (Ding et al., 2002). $p12^{I}$ interaction with calcineurin and calreticulin results in retention

of the calreticulin-MHC-I complexes in the ER or *cis*-Golgi leading to the inhibition of its association with β2-micro-globulin and subsequent trafficking to the cell surface (Johnson et al., 2000). Furthermore, expression of $p12^{I}$ in Jurkat T cells resulted in a calcium-dependent increase in expression of transcriptional co-activator p300 and p300-dependent transcription resulting in T cell activation and efficient viral infection (Nair et al., 2006).

3.5 Enteroviruses

Enteroviruses are non-enveloped RNA viruses such as poliovirus and coxsackievirus. Enteroviral infections are associated with many human diseases such as aseptic meningitis, hand-foot and mouth disease, paralysis and myocarditis. Enterovirus 2B protein is a viroporin that can enhance membrane permeability by forming membrane lesions on the ER and plasma membrane. The 2B protein has been implicated in disruption of intracellular Ca^{2+} homeostasis via depletion of ER Ca^{2+} stores and elevation of cytosolic Ca^{2+} concentration (Peischard et al., 2019; van Kuppeveld et al., 2005). Infection with poliovirus and coxsackievirus is shown to increase cytosolic Ca^{2+} concentration partly through its release from ER via IP3R and RyR channels and subsequent uptake by mitochondria through Ca^{2+} uniporter and VDAC, resulting in high mitochondrial Ca^{2+} overload, mitochondrial dysfunction and apoptosis (Brisac et al., 2010; Peischard et al., 2019). Similarly, coxsackievirus infection is associated with 2B protein-mediated release of Ca^{2+} from the ER and Golgi stores with a concomitant increase in extracellular Ca^{2+} uptake. This leads to a decline in the Ca^{2+} release capacity of the intracellular stores and inhibition of stimulus-induced mitochondrial uptake of Ca^{2+} resulting in perturbation of overall intracellular Ca^{2+} homeostasis (Campanella et al., 2004; van Kuppeveld et al., 1997). The 2B protein-mediated decline in ER and Golgi Ca^{2+} load is also implicated in disrupting the Golgi secretory trafficking resulting in inhibition of cytokine release, recycling of receptors and antigen presentation, thereby affecting the innate and adaptive immune responses during infection (de Jong et al., 2006). The disruption of intracellular Ca^{2+} homeostasis also leads to a decline in mitochondrial ATP production capacity and induction of autophagy via activation of the AMPK/MEK/ERK and Ras/Raf/MEK/ERK signaling pathways facilitating enterovirus pathogenesis (Xin et al., 2015). Some groups also report antiapoptotic function of 2B due to disruption of apoptotic signaling between ER and mitochondria as a consequence of reduced Ca^{2+} concentration in ER (Campanella et al., 2004). With the global disruption of intracellular Ca^{2+} homeostasis during enterovirus infection, what fine-tunes the switch from proapoptotic to antiapoptotic signaling remains an enigma. Infection of coxsackievirus also perturbs mitochondrial metabolism and infection of mouse cardiomyocytes with coxsackievirus B3 showed decreased activities of ETC complexes I and III causing cardiac insufficiency (Peischard et al., 2019).

3.6 Kaposi’s sarcoma associated herpesvirus (KHSV)

KSHV, also termed Human Herpesvirus 8 (HHV8), infects circulating B cells and endothelial cells and causes Kaposi’s sarcoma, primary effusion lymphoma and a subset of Castleman’s disease. KHSV infection is known to perturb cellular Ca^{2+} homeostasis and several of its proteins, K15, v-GPCR, K1, K7, VMIP I and II and v-Bcl2 contribute to this. The K1 protein of KHSV is a B cell receptor-like protein that triggers a downstream cascade of tyrosine phosphorylation leading to a prolonged increase in intracellular Ca^{2+}

concentration resulting in NFAT activation, upregulation of inflammatory cytokines and viral dissemination (Lee et al., 2005). The KHSV protein K7 localizes to the mitochondria and maintains mitochondrial membrane potential. It induces cytoplasmic Ca^{2+} mobilization by promoting ER Ca^{2+} release and activation of capacitative Ca^{2+} entry (CCE) via its interaction with cellular Calcium-Modulating Cyclophilin Ligand (CAML). As a result, increased cytosolic calcium levels prevent cellular apoptosis and enable the successful completion of viral replication (Feng et al., 2002). Intracellular calcium mobilization was shown to trigger expression of lytic viral accessory protein PF-8 or the late-lytic viral envelope glycoprotein gpK8 through calcineurin resulting in reactivation of latent KHSV infection (Zoeteweij et al., 2001). KHSV encoded v-Bcl2, which shares structural and functional homology with Bcl-2, promotes viral persistence, latency and development of Kaposi sarcoma by enhancing the viability of infected cells (Boshoff and Chang, 2001).

3.7 Human herpes Simplex viruses (HSV)

Herpes Simplex Virus type-1 and 2 (HSV-1 and HSV-2) are wide-spread across the globe and lead to lifelong infections. HSV1 is usually associated with oral sores and HSV2 infection leads to genital herpes. HSV-1 and HSV-2 infection has been shown to result in a rapid transient increase in cytosolic Ca^{2+} concentration through release from IP3-sensitive ER stores. This increase in cytosolic Ca^{2+} levels leads to FAK phosphorylation and reorganization of the actin cytoskeleton facilitating the nuclear trafficking of internalized virus (Chami et al., 2006; Cheshenko et al., 2003). In HSV-1 infected macrophages, an increase in cytosolic Ca^{2+} levels due to release from mitochondria results in activation of NFkB ultimately leading to the enhancement of proinflammatory responses (Mogensen et al., 2003). Increased cytosolic Ca^{2+} levels also lead to cell death and virus release thereby helping in the spread of HSV-1 infection (Yura et al., 2003). HSV-2 glycoprotein H has been shown to interact with integrin $\alpha v\beta 3$ and promote the release of Ca^{2+} from intracellular stores which facilitate viral entry and dissemination (Cheshenko et al., 2014).

3.8 Influenza a virus (IAV)

Influenza A virus (IAV) infection of neurons and neutrophils is shown to promote Ca^{2+} release from ER stores through activation of IP3R pathway resulting in an increase in cytosolic Ca^{2+} overload and disruption in neuronal and neutrophil physiology (Brask et al., 2001; Hartshorn et al., 1988). The L-type channel, Cav1.2 serves as a receptor for IAV binding and entry and chemical inhibition or knockdown of voltage-gated calcium channels inhibited H1N1 and H3N2 IAV infection in multiple cell lines (Chandrasekaran et al., 2008; Fujioka et al., 2018). Influenza virus protein PB1-F2 has been shown to localize to the mitochondria and triggers mitochondrial depolarization and apoptosis (Chanturiya et al., 2004). Synthetic liposomes harboring the PB1-F2 suggest that it facilitates Ca^{2+} conductance and functions as a canonical channel for the conductance of cations and anions with low selectivity (Henkel et al., 2010).

3.9 Epstein-Barr virus (EBV)

EBV, also known as human herpesvirus 4 is among the most common human virus and associated with benign and malignant tumors of epithelial and lymphoid cells. EBV entry into the cells is dependent on host cell calcium. Verapamil, an L-type Ca^{2+} channel blocker

is effective in inhibiting EBV entry and EBV-mediated transformation of B cells (Dugas et al., 1988). During latent infection, EBV expresses the latent membrane protein 2A (LMP2A) which aggregates on the plasma membrane and mimics B cell receptor and prevents calcium mobilization upon B cell stimulation by competitively binding to the cellular phospho-tyrosine kinases (PTKs) (Fruehling and Longnecker, 1997; Miller et al., 1994, 1993).

EBV oncoprotein latent membrane protein 1 (LMP1) reactivates EBV in a calcium-dependent manner via Ca^{2+}/calmodulin dependent protein kinase type IV/Gr (CaMKIV/Gr) mediated upregulation of the transcription of transcriptional activators of the lytic phase through their calcium-responsive sites in promoter regions (Chatila et al., 1997; Liu et al., 1997; Mosialos et al., 1994)

3.10 Ebola virus (EBOV)

EBOV is a deadly RNA virus that causes the lethal Ebola hemorrhagic fever. Infection with EBOV affects the endolysosomal calcium Two Pore Channels (TPCs) resulting in increased cytosolic Ca^{2+} levels through release from endolysosomal stores. This Ca^{2+} influx into cytosol facilitates intracellular trafficking of virus-containing endosomal vesicles. Disruption of TPC function by genetic knockout or chemical inhibition was effective in inhibiting virus entry (Sakurai et al., 2015). Inhibition of Ca^{2+} release from endolysosomal stores by small molecule antagonist like Ned19, NAADP and tetrandrine inhibits EBOV infection of macrophages (Sakurai et al., 2015). In addition, EBOV, Marburg virus (MARV) and Junin virus (JUNV) have also been implicated in STIM1/ORAI1-mediated calcium signaling to facilitate their budding and egress from host cells (Han et al., 2015).

3.11 Rotavirus (RV)

Rotavirus is a non-enveloped RNA virus that causes viral gastroenteritis. Many studies implicate the role of Ca^{2+} in the cytopathology of infected enterocytes. Ca^{2+} chelation with BAPTA, blocking L-type Ca^{2+} channel with verapamil and reduction in extracellular Ca^{2+} concentration are protective against rotavirus-associated cytopathy. NSP4 protein of this virus acts as an enterotoxin that elevates cytosolic Ca^{2+} concentration due to phospholipase C activation and IP3 production (Dong et al., 1997; Tian et al., 1995). Also, activation of L-type Ca^{2+} channel has been shown to serve in increasing cytosolic Ca^{2+} concentration. Studies have shown that the initial increase in cytosolic Ca^{2+} was due to increased permeability of cell membrane, whereas both extracellular Ca^{2+} influx and release from ER-Ca^{2+} stores contribute to the later elevation in cytosolic Ca^{2+} concentration (Brunet et al., 2000). Moreover, the release of Ca^{2+} from ER, impairs N-glycosylation of rotavirus proteins VP7 and NSP4 and has been implicated in cell death (Poruchynsky et al., 1991).

3.12 Other viruses

Tulane virus (TV), a rhesus enteric calicivirus disrupts Ca^{2+} homeostasis and high cytosolic Ca^{2+} levels is important for its replication. The TV NS1-2 protein has a characteristic viroporin domain (VPD) and functions like a viroporin. It localizes to the ER and causes aberrant Ca^{2+} signaling when expressed in mammalian cells and truncation of the VP domain abrogated these functions of NSP1-2 (Strtak et al., 2019). Similarly, human

cytomegalovirus (HCMV) also increases intracellular Ca^{2+} levels to favor virus replication by triggering the depletion of ER Ca^{2+} stores via the viral protein UL37X1 mediated activation of host's P2Y2 purinergic receptors and PLC-IP_3 pathway (Chen et al., 2019a). Further murine cytomegalovirus (MCMV) is shown to significantly alter cytoplasmic Ca^{2+} level and MMP in mice cochlear neurons (Panel et al., 2019).

Japanese encephalitis virus (JEV) is an arbovirus that is the most common agent of acute viral encephalitis in South-East Asia. JEV infection increases intracellular Ca^{2+} levels and disrupts mitochondrial membrane potential (MMP). Treatment of infected cells with CW-33, a synthesized derivative of furoquinolines reduced intracellular Ca^{2+} levels, raised mitochondrial membrane potential, and upregulated anti-apoptotic signaling pathways of AKT/mTOR. Besides, CW-33 activated the expression of IFN-stimulated genes (ISGs). Results demonstrate that the CW-33 exhibits significant potential against JEV (Huang et al., 2016).

Chandipura virus (CHPV), another neurotropic virus associated with acute viral encephalitis and is shown to promote neuronal cell death by disrupting intracellular Ca^{2+} signaling which leads to mitochondrial dysfunction and oxidative stress leading to neuronal apoptosis through the FasL-FADD pathway during CHPV infection. Minocycline, a broad-spectrum antibiotic with anti-oxidative and anti-inflammatory properties was found to be effective in mitigating the increase in cytoplasmic $Ca+^{2}$ and ROS levels and CHPV induced cellular apoptosis (Verma et al., 2018)

Dengue virus (DENV) is shown to promote colocalization of STIM1 and ORAI1 leading to their interaction and activation of store operated Ca^{2+} entry (SOCE). Manipulation of the intracellular and extracellular Ca^{2+} levels by Ca^{2+} chelators SOC inhibitor SKF96365 decreased DENV yield suggesting that DENV alters cellular Ca^{2+} homeostasis to favor viral replication and dissemination (Cheshenko et al., 2007; Dionicio et al., 2018). Many viruses have also been shown to depend on STIM1 and ORAI1 interaction and Ca^{2+} signaling for the budding and egress of mature virus particles (Chen and Lamb, 2008; Chen et al., 2019b; Freedman and Harty, 2016; Han et al., 2015; Yao et al., 2018). The expression of several TRP channels like TRPV1, TRPA1 and TRPM8 is increased during infection with respiratory viruses such as respiratory syncytial virus (RSV), measles virus (MV) and human rhinovirus (HRV). While the increase in expression of TRPA1 and TRPV1 is mediated by soluble factors released during viral infections, enhanced expression of TRPM8 is dependent on virus replication. These findings provide insights into the possible utilization of these TRP channels by respiratory viruses to create a favorable intracellular Ca^{2+} environment to favor their replication (Abdullah et al., 2014; Omar et al., 2017).

Parvovirus VP1 protein is also shown to increase cytosolic Ca^{2+} concentration by mediating the activation of I_{CRAC} channels of the plasma membrane (Nykky et al., 2014).

Porcine Delta Corona Virus (PDCoV), an enteropathogenic virus that causes severe vomiting and diarrhea in infected piglets upregulates intracellular Ca^{2+} concentrations which cause calpain-mediated lysosomal disruption with subsequent release of cathepsin B and L. Upregulated expression of cathepsin L and B facilitate virus infection and L-type Ca^{2+}

channel blocker diltiazem hydrochloride significantly inhibited PDCoV infection (Zhang et al., 2019b).

Like EBOV, Middle East Respiratory Syndrome Corona Virus (MERS-CoV) also utilizes the NAADP dependent TPC channels for Ca^{2+} mobilization from the endolysosomal stores to facilitate viral entry and trafficking (Gunaratne et al., 2018).

We have briefly summarized the cytobiological effects on Ca^{2+} signaling induced by specific viral proteins or the complete viral particle in the following Table 1.

4 ER-Mitochondria calcium signaling in cellular stress responses

Ca^{2+} plays a central role in many cell-signaling pathways and hence the regulation of cellular Ca^{2+} homeostasis is crucial for cell survival and function. Ca^{2+} homeostasis is ensured by coordinated efforts of the Ca^{2+} channels, binding, transport, sensor and buffer proteins, including the cellular organelles that serve as Ca^{2+} stores to manage/buffer the transient spikes in intracellular Ca^{2+}.

The ER comprises a major part of the cellular reticular network, which is involved in many vital processes in the cell including Ca^{2+} homeostasis. Disruption in ER function upregulates the ER stress responses such as the Unfolded Protein Response (UPR). The upregulation of UPR results in the immediate shutdown of protein translation, enhanced transcription of genes that encode proteins that enhance ER protein folding capacity and ER-Associated Degradation (ERAD) of misfolded proteins. If the ER stress is beyond the threshold of repair UPR also activates the cell death pathways. The integral membrane proteins of ER, dsDNA activated protein kinase R like ER-resident kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1) orchestrate the transduction of ER stress signal and activation of UPR. This important topic has been covered in substantial detail by many good reviews (Hetz and Glimcher, 2009; Ron and Walter, 2007). In this review, we will focus on the integral role of cellular Ca^{2+} signaling in the modulation of ER stress responses.

Thapsigargin, an inhibitor of SERCA is a widely used compound to induce ER stress suggesting that disturbance in ER Ca^{2+} homeostasis directly contributes to ER stress. ER Ca^{2+} depletion results in rapid accumulation of misfolded proteins in the ER and UPR activation due to disruption in the activity of the ER chaperones and folding proteins such as calreticulin, BiP and protein disulfide isomerase. In addition to the requirement of Ca^{2+} for their effective function, these proteins also contribute to Ca^{2+} buffering in ER lumen hence promote ER Ca^{2+} homeostasis. The Ca^{2+} dependent immunoglobulin binding protein (BiP) plays a very central role in this process as it is involved in sensing misfolded proteins and activation of the ER stress transducers. Calreticulin, the ER chaperone and Ca^{2+} buffer is also known to co-ordinate with BiP to maintain ATF6 in an inactive state and during ER stress it dissociates from ATF6 to promote UPR activation (Hong et al., 2004). Upon depletion of ER Ca^{2+}, an ER-resident oxidoreductase PDIA6 has been shown to stimulate IRE1 activity by interacting with its ER luminal domain. PDIA6 expression is tightly regulated by microRNA-322 and an increase in cytosolic Ca^{2+} concentration

through depletion of ER Ca^{2+} stores and SOCE reduces miR-322 abundance, thereby increasing PD1A6 levels (Groenendyk et al., 2014). Lipid overload during obesity may lead to increased delivery of saturated fatty acids to the ER which has been shown to enhance saturation of the ER phospholipids and direct activation of UPR transducers PERK and IRE1. Similarly, enhanced delivery of unesterified cholesterol to ER leads to inhibition of SERCA ATPase resulting in disruption of ER Ca^{2+} homeostasis and UPR activation (Li et al., 2004; Volmer et al., 2013).

Disruption in ER Ca^{2+} homeostasis disrupts mitochondrial functions due to calcium overload thereby affecting mitochondrial bioenergetics and lipid metabolism. The mitochondrial Ca^{2+} uniporter-dependent uptake of Ca^{2+} released from ER stores at the contact sites is shown to be facilitated by the mitochondrial fusion protein, Mitofusin 2 (Mfn2) (de Brito and Scorrano, 2008). Mfn2 is enriched in these contact sites and an optimum level of Mfn2 expression is required to facilitate proper interaction between ER and mitochondria and smooth Ca^{2+} transport (Guo et al., 2007). Under normal physiological conditions, the Bcl2 family anti-apoptotic protein localizes to the ER membrane and preserves ER luminal Ca^{2+} concentration by regulating IP3R mediated ER Ca^{2+} release and the Bcl2 family pro-apoptotic proteins have been implicated in reduced ER luminal Ca^{2+} concentration. Few studies also suggest that these Bcl2 family proteins also interact with SERCA to modulate Ca^{2+} uptake and release from ER (Lewis et al., 2014). Signaling pathways that are activated in ER stress responses have also been implicated to promote autophagy. Besides, ER Ca^{2+} release or SOCE can result in high cytosolic Ca^{2+} concentrations which activate CamKKβ leading to AMPK mediated mTOR inhibition and activation of autophagy (Decuypere et al., 2013; Høyer-Hansen et al., 2007). On the other hand, Ca^{2+} overloading in mitochondria can promote mitochondrial dysfunction and injury subsequently leading to activation of PINK1-PARKIN mediated mitochondrial-selective autophagy or Mitophagy (Chen and Dorn, 2013). Thus, the dynamics of ER-mitochondrial calcium transport govern overall cellular homeostasis and perturbation in this process has been implicated in many chronic and debilitating human diseases (Krebs et al., 2015).

4.1 Ca^{2+} signaling in cellular innate immune and antiviral signaling

The crucial role of calcium in immune cell function and activation of resting immune cells is well defined. Here, we will review the significance of ER-mitochondrial calcium signaling in the cellular innate immune response against viral infections. The cellular antiviral response is activated upon pathogen recognition by Pathogen Associated Molecular Patterns (PAMPs) via an array of Pathogen Recognition Receptors (PRRs). The activation of PRRs triggers a cascade of signaling events that promote the production of type-1 interferons which then activate the antiviral signaling in paracrine and autocrine mode to trigger transcription of antiviral genes (Brubaker et al., 2015). Most studied PRRs include Toll-like Receptors (TLRs), Retinoic Acid-Inducible Gene I (RIG1) like Receptors (RLRs), Nucleotide-binding Oligomerization Domain (NOD)-Like Receptors (NLRs) and cyclic GMP-AMP (cGAMP) synthase (cGAS) (Refolo et al., 2020; Streicher and Jouvenet, 2019). In this section, we will discuss the modulation of the receptor-induced antiviral responses via intracellular Ca^{2+} signaling.

4.1.1 Calcium mediated modulation of TLR signaling—TLRs are one of the important receptors of the innate immune system recognizing PAMPs expressed on the surface of invading microbial pathogens. Post activation, TLRs promote inositol-1, 4, 5-trisphosphate (IP3) and diacylglycerol production giving rise to a cascade of events which lead to the release of Ca^{2+} from the ER lumen thereby reducing the load of ER Ca^{2+} stores (Feske et al., 2012; Hogan et al., 2010). The reduced Ca^{2+} concentration in ER lumen leads to the confirmational change in Stromal Interaction Molecule1 (STIM1) an ER Ca^{2+} sensor on the ER membrane which results in its interaction with calcium release-activated calcium channel protein 1 (ORAI1) located on the plasma membrane thereby opening Ca^{2+} permeable ORAI1 ion channels to initiate Ca^{2+} entry (Feske et al., 2012; Hogan et al., 2010). Once activated the TLRs rapidly activate the extracellular signal-regulated kinase (ERK1/2) pathway by coordinating GTPases Ras and Rap1 activation in immune cells which stimulate the production of inflammatory cytokines and chemokines (Feske et al., 2012; Hogan et al., 2010; Tang et al., 2017, 2015). The entry of Ca^{2+} effected the activation of ERK1/2 (Limnander and Weiss, 2011) suggesting that Ca^{2+} may play an essential role in regulating the activation of ERK1/2 triggered by TLRs (Tang et al., 2015). A study on human Mesenchymal Stem Cells (hMSCs) showed TLR3/4 priming results in the induction of cytokines (IFNs and interleukins) that are closely dependent on intracellular Ca^{2+} signaling (Park et al., 2016). The high concentration of Ca^{2+} induces dsRNA sensors like TLR3, MDA5 and RIG-I in epidermal keratinocytes. Other TLRs (TLR1 and 2) and IFNα are also induced in response to high Ca^{2+}. It also enhances antiviral activity of epidermal keratinocytes by upregulating Human β-Defensins 2 and 3 (HBD2 & HBD3) in response to HSV1 infection (Yamamura et al., 2018).

4.1.2 Calcium mediated modulation of RLR signaling—Viral infection can induce IFN response and ER stress simultaneously. ER stress can directly contribute to mitochondrial dysfunction by Ca^{2+} overload and ROS accumulation and perturb mitochondrial antiviral signaling (Csordás and Hajnóczky, 2009; West et al., 2011). The mitochondria serve as a hub for orchestrating the cellular antiviral signaling mediated by RIG-I-like Receptors (RLR). RIG-I-like receptor family belongs to a class of PRRs that responds to RNA virus infections and comprises three helicases namely Retinoic-Inducible Gene-I (RIG-I), Melanoma Differentiation-Associated gene 5 (MDA5) and Laboratory of Genetics and Physiology 2 (LGP2). RIG-I and MDA5 contain a helicase domain and N-terminal Caspase Recruitment Domain (CARD). Through the CARD-CARD interaction, the RLR proteins interact with the mitochondrial antiviral signaling (MAVS) protein on the mitochondrial outer membrane leading to the activation of the IRF3 and NFκB pathways (Jacobs and Coyne, 2013). It has been demonstrated that ER stress further enhances interferon β production upon stimulation with ISGs and the mitochondrial calcium uniporter interacts with MAVS. Knockout of MCU indicated that MCU positively regulates RLR signaling and MAVS-dependent IFNβ production during ER stress conditions (Cheng et al., 2016). The reduced mitochondrial potential has also been implicated in reduced anti-viral signaling due to its negative effect on MAVS signaling (Koshiba et al., 2011). Dissipation of mitochondrial membrane potential did not disrupt the signaling downstream of MAVS suggesting the mitochondrial function and homeostasis likely affect RLR signaling at the MAVS level (Koshiba et al., 2011). The viruses may exploit this aspect by increasing ER

Ca^{2+} depletion and uptake by mitochondria to disrupt mitochondrial membrane potential and negatively affect RLR signaling and host antiviral response.

4.1.3 Calcium mediated modulation of inflammasome activation—NOD-like Receptor Protein 3 (NLRP3) inflammasome is a multimeric protein complex that triggers the release of proinflammatory cytokines IL-1β and IL-18. A wide variety of agents and DAMPs, such as silica and uric acid crystals and PAMPS such as dsDNA activate the NLRP3 inflammasome. The Calcium Sensing Receptor (CASR) activates the NLRP3 inflammasome through phospholipase C, which catalyzes IP3 production and thereby induces the release of Ca^{2+} from ER stores leading to a decrease in cAMP concentration and activation of NLRP3 inflammasome (Guo et al., 2015; Horng, 2014; Lee et al., 2012). Additionally, Ca^{2+} release from ER and influx through plasma membrane induces mitochondrial damage, ROS production, MMP loss and mitochondrial DNA release to the cytosol, activating the NLRP3 inflammasome. Inflammasome complex in turn helps in cytokine maturation (majorly proinflammatory cytokines IL1β and IL-18) via proteolytic processing by caspase 1 (Murakami et al., 2012). The above-mentioned studies also unraveled the role of NLRP3 inflammasome activators like ATP and Nigericin in promoting ER Ca^{2+} release via IP3R and other Ca^{2+} channels that in turn result in activation of the complex (Lee et al., 2012; Murakami et al., 2012). However, along with the direct involvement of Ca^{2+} signaling, there are additional regulators of Ca^{2+} related signaling pathways like TRP channels (TRPV2 and TRPM2) that also play a role in modulating NLRP3 inflammasome activation (Compan et al., 2012; Elliott and Sutterwala, 2015; Zhong et al., 2013). These findings strengthen the fact that ER-mitochondrial Ca^{2+} signaling is a key modulator of NLRP3 inflammasome-mediated innate immune response.

4.1.4 Calcium mediated modulation of STING activity—STING (Stimulator of IFN Genes) is a member of the ISGs (Interferon Stimulating Genes) family that plays a crucial role in host IFN response against pathogens. Ca^{2+} chelator (BAPTA-AM) suppresses IRF3 activation and IFN production via inhibition of STING translocation from ER to the cytoplasm (Hirabayashi et al., 2017) suggesting the role of intra-cellular Ca^{2+} in STING signaling. During viral infections (HSV1 and HCMV) increase in intracellular Ca^{2+} may activate STING via multiple pathways. High Ca^{2+} levels are sensed by Calmodulin (CaM) that phosphorylates CaMKII and AMPK. They in turn suppress ULK1 (inhibitor of STING) phosphorylation activating STING. Activated CaMKII and AMPK also phosphorylate Beclin 1 that induces autophagy and STING. Using Sendai virus and HCMV particles, it was demonstrated that virus entry and fusion with endosomal membranes induce cytoplasmic Ca^{2+} oscillations and disruption of Ca^{2+} signaling with 2-APB completely blocking the antiviral activity by inhibiting the relocation of STING from ER to the cytoplasm as well as nuclear translocation of IRF3 suggesting that Ca^{2+} is required for STING activation in the response to HCMV infection (Hare et al., 2015). Enhanced intracellular Ca^{2+} also triggers loss of mitochondrial membrane potential and opening of mPTP resulting in the leakage of mtDNA into the cytosol. This is sensed by cGAS that gets activated and in turn leads to STING activation (Hare et al., 2015; Holm et al., 2012; Mathavarajah et al., 2019; Sharon-Friling and Shenk, 2014). A study on mouse macrophages indicates that STIM1 (an ER Ca^{2+} sensor) interacts with STING resulting in its activation

to trigger IFN response (Srikanth et al., 2019). In this context, it is important to note that STING also tightly regulates Ca^{2+} fluxes in association with SERCA2 (Mathavarajah et al., 2019).

4.2 Modulation of innate immune signaling via autophagy induction

Autophagy plays a crucial role in defense against intracellular pathogens and many viral pathogens are also known to exploit autophagy for their benefit. Ca^{2+} is crucial for autophagic induction however it is unclear if an increase in cytosolic Ca^{2+} levels or modifications of ER Ca^{2+} levels contributes to the induction of autophagy (Brady et al., 2007; Gao et al., 2008; Gordon et al., 1993; Høyer-Hansen et al., 2007). During stress conditions like starvation, Ca^{2+} released from lysosomes activates the Transcription Factor EB (TFEB) by a calcium-dependent phosphatase, Calcineurin. TFEB migrates to the nucleus to activate the expression of autophagic pathway genes (Medina et al., 2015). On the other hand, deregulation of IP3R mediated Ca^{2+} signaling reduces mitochondrial Ca^{2+} uptake, amputates OXPHOS and stimulates autophagy due to activation of AMPK. IP3R also regulates autophagy through its interaction with Beclin-1. IP3R antagonist, Xestospongin B induces autophagy by disrupting the molecular complex formed by IP3R and Beclin 1 (Cárdenas et al., 2010; Decuypere et al., 2011; Vicencio et al., 2009).

With all these facts, Ca^{2+} signaling proves to be a major modulator of host innate immune responses towards many pathogens and hence can be a potent target for developing therapeutic approaches.

5 Mitochondrial Ca^{2+} signaling as a therapeutic target

Ca^{2+} being the central player in cellular bioenergetics as well as organelle homeostasis, can be explored as a potential therapeutic target against innumerable human diseases including those manifested upon pathogen infestation. Owing to its role in many host cellular pathways, its modulation will be a better approach in the development of a broad spectrum drug against many human illnesses. The anti-JEV compound CW33, reduces mitochondrial Ca^{2+} overload and stabilizes membrane potential via activation of Akt/mTOR and Jak/STAT1 pathway in JEV infected BHK21 cells. It further activates the GTPases and induces STAT1 mediated antiviral response against JEV (Huang et al., 2016). During HBV infection, cytosolic Ca^{2+} dependent Proline-rich tyrosine Kinase (PyK2) is activated by HBV X protein that enhances viral DNA replication and assembly (Bouchard et al., 2001; Choi et al., 2005; Zhang et al., 2016). A specific L-type Ca^{2+} channel blocker Oxethazaine, generally used as a gastric pain reliever is found to significantly decrease cytosolic Ca^{2+} concentration and thereby inhibits PyK2 mediated HBV replication and capsid assembly. Anti-influenza compound Amantadine ameliorates HCV proteins induced mitochondrial dysfunction and nitro oxidative stress via prevention of mitochondrial Ca^{2+} overload, ROS production, induction of mitochondrial hyperpolarization and delaying Ca^{2+} induced mPTP opening (Piccoli et al., 2009; Quarato et al., 2014). In addition to Amantadine, another antiviral drug Alisporivir also prevents HCV-induced mitochondrial Ca^{2+} overload, enhances cellular respiration and limits ROS production. Being a Cyclophilin D inhibitor, it also reverts HCV-induced mitochondrial dysfunction via blocking Cyclophilin D interaction with

mPTP and desensitizing its opening (Quarato et al., 2012). MicroRNA 222 downregulates Thrombospondin-1 (THBS1) and Cluster of Differentiation 47 (CD47) expression which are known to induce mitochondrial dysfunction by modulating mitochondrial Ca^{2+} level and MMP upon Transmissible Gastro Enterovirus (TGEV) infection (Zhao et al., 2019). Hepatic ischemia/reperfusion injury includes mitochondrial dysfunction as a result of mPTP opening. A study involving an array of small molecule inhibitors of cyclophilin D suggested these inhibitors prevent mPTP opening in hepatocytes, thus restoring the hepatocytes Ca^{2+} retention capacity, oxidative phosphorylation and reduced liver damage in diseased cellular as well as animal model (Panel et al., 2019). An anti-inflammatory and anti-oxidative agent Minocycline has Ca^{2+} chelating property that is proved useful in normalizing CHPV induced cytoplasmic Ca^{2+} levels thereby limiting ROS production and p38 phosphorylation that otherwise leads to activation of the apoptotic cascade (Verma et al., 2018). Neurotrophins are proved to protect neurons against HIV infection mediated destabilization of Ca^{2+} homeostasis and oxidative stress. LM11A-31 is a novel non-peptide that mimics a p75 neurotrophin receptor ligand-binding domain of nerve growth factor (NGF). LM11A-31 stabilizes Ca^{2+} homeostasis and prevents the development of disease conditions in HIV-infected neurons by PI3K-dependent activation of AKT1 signaling (Meeker et al., 2016). Ebola virus entry into host cells is dependent on the host endosomal Two Pore Channel (TPC). Tetrandrine is a small molecule inhibitor of the TPC channel that restricts Ebola virus entry and infection in macrophages as well as *in vivo* models (Sakurai et al., 2015). A study on mitochondrial Ca^{2+} stabilization hypothesizes a hybrid trifunctional neuroprotective compound possessing the ability to ameliorate the deregulation of Ca^{2+} dynamics during certain diseases like Alzheimer's. It contains three different moieties for regulation of different Ca^{2+} related pathways; (i) a dihydropyridine moiety to block L type Ca^{2+}channels restricting Ca^{2+} entry, (ii) a benzothiazepine moiety to block NCLX and slow down Ca^{2+} efflux from mitochondria, and (iii) a polyphenol moiety to mask excess free radicals. This leads to delayed apoptosis and can act as an effective neuroprotector useful in treating Alzheimer's by delaying disease progression (Fernández-Morales et al., 2012).

In addition to these approved drug molecules and newly synthesized chemical compounds, certain host factors play a protective role against the deregulation of Ca^{2+} homeostasis. Forkhead box O3a (FOXO3a) is a transcription factor that up-regulates Bcl2/adenovirus F1B 19KDa protein Interacting Protein 3 (BNIP3) expression in adult cardiomyocytes that results in increased mitochondrial Ca^{2+} leading to MMP loss, mitochondrial fragmentation and apoptosis. dn-FX3a, an Adeno associated virus encoding dominant-negative FOXO3a is proved to attenuate BNIP3 expression and improves mitochondrial structure and function (Chaanine et al., 2016) in normal as well as stressed cardiomyocytes. Hax1 is another host factor localized in the cytosolic surface of ER and mitochondria (Yap et al., 2011) that regulates Ca^{2+} signaling and inhibits apoptosis (Li et al., 2009). It is the central regulator of ER Ca^{2+} storage in interaction with Ca^{2+} pumps. HIV and CSFV virus proteins interact with Hax1 and disrupt its localization pattern and induce cell death (Jacotot et al., 2000). Hax1 also regulates lymphocyte development, trafficking and survival (Chao et al., 2008). Deregulation of the same is seen in cases of cancer, neurological disorder and psoriasis (Simmen, 2011). Taking into account their importance in cellular Ca^{2+} homeostasis and associated functions, both FOXO3a and Hax1 can be explored as potential

targets for therapeutics development against certain diseases resulting from Ca^{2+} signaling deregulation.

Certain pharmacological modulators have been found to regulate Ca^{2+} transport, dynamics, and homeostasis during preliminary research. However, their role as potential therapeutics against human diseases needs further research. Ruthenium Red (RuR/ Ru360) reduces Ca^{2+} uptake and mitochondrial Ca^{2+} overload (García-Rivas et al., 2006). Veratridine treatment enhances mitochondrial Ca^{2+} accumulation, oxidative stress and p38-MAPK linked neural cell death in mouse hippocampal slices. CGP-37157 is a mitochondrial NCLX channel inhibitor that regulates the mitochondrial Ca^{2+} level, cellular energy metabolism and rescues neurons from veratridine induced death (Nicolau et al., 2010). CGP-37157 also affects Ca^{2+} transport by affecting mRyR, SERCA pump in striated muscles, inhibiting L type Ca^{2+} channel in β cells and modulating VGCC in neurons (Neumann et al., 2011). Certain Benzodiazepines and Benzothiazepines like Clonazepam and Diltiazem respectively also inhibit L type Ca^{2+} channel in the plasma membrane (Kinnally et al., 1993). Another *in silico* study including 700 FDA-approved drugs, suggests Mitoxanthone to specifically inhibit Ca^{2+} uptake by MCU without affecting mitochondrial bioenergetics (Arduino and Perocchi, 2018). Dantrolene, an antispasmodic drug inhibits ER Ca^{2+} channels and limits Ca^{2+} accumulation (Piccoli et al., 2007). Acyclovir blocks mitochondrial permeability transition pore and thus restricts deregulated leakage across the mitochondrial membrane that leads to apoptosis (Scrima et al., 2018). Though these compounds are effective in preserving mitochondrial Ca^{2+} homeostasis, their *in vivo* application is still under question. There are certain limitations like lack of specificity, interference with the function of other organelles and inadequate efficiency that demands further research for its clinical validation and usage.

6 Conclusion and future perspectives

Ca^{2+} is an indispensable ion for almost every cellular process and is tightly maintained in a state of homeostasis. Perturbances in cellular Ca^{2+} homeostasis have been implicated in many human pathologies and infectious diseases. Many viruses target cellular Ca^{2+} homeostasis to proliferate and disseminate successfully. The broad range of intracellular Ca^{2+} concentrations across membranes enable the viruses to make subtle changes in Ca^{2+} concentrations for their own benefit without major detrimental effects to the host cells. Targeting cellular Ca^{2+} signaling is an attractive therapeutic option to curb viral infections and counteract viral disease pathogenesis. It has to be noted that Ca^{2+} is pivotal for many cellular processes and therapeutics targeting Ca^{2+} signaling may have detrimental and toxic effects. However, being a major target of many viruses, modulation of cellular Ca^{2+} signaling may have a broad antiviral effect and facilitate development of panantivirals. Due to its function as a central node of multiple signaling events, understanding the direct effect of Ca^{2+} perturbations during viral infections has been a challenge and needs further detailed investigations. The transient and rapid spatiotemporal changes in Ca^{2+} concentration and signaling urge for development of more specific and flexible tools to investigate Ca^{2+} signaling pathways and unravel the precise mechanisms involved. Many FDA approved drugs targeting specific Ca^{2+} signaling components are already in use to treat several human

pathological conditions. The probable repurposing of such drugs may be an attractive option to rapidly develop cost-effective antiviral therapeutics targeting the Ca^{2+} signaling.

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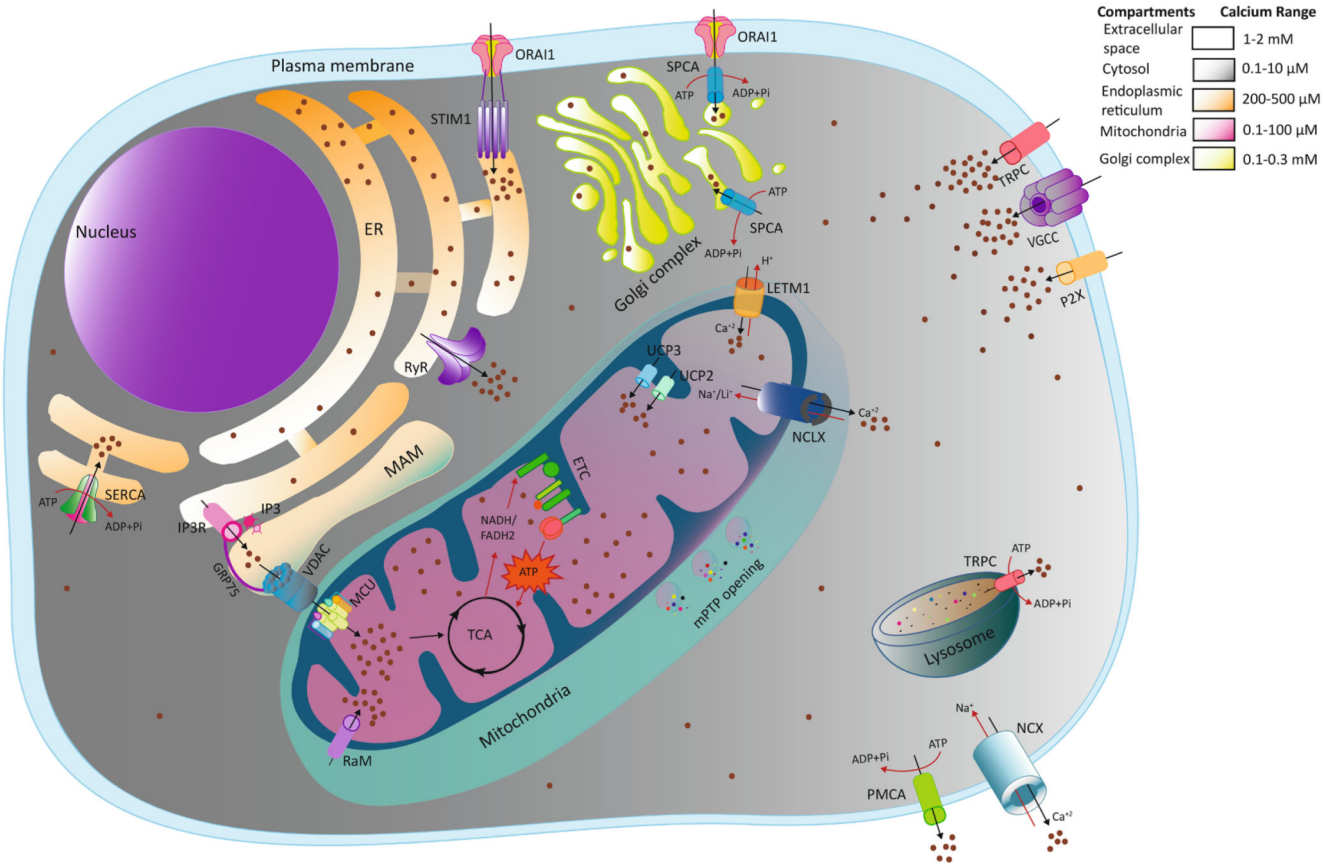

Fig. 1. Model depicting cellular calcium trafficking.

Calcium migrates from the extracellular matrix (high Ca^{2+} concentration) to cytosol (low Ca^{2+} concentration) across plasma membrane via Voltage-Gated Calcium Channels (VGCCs), Transient Receptor potential Channels (TRPs) and Purinergic receptors (P2Xs). Intracellular stores like ER replenish the depleted Ca^{2+} level directly through plasma membrane transport via the ORAI1-STIM1 complex, otherwise known as Store-operated Calcium Entry (SOCE). Sarco-Endoplasmic Reticulum Calcium ATPase (SERCA) also maintains the basal ER Ca^{2+} level by ATP-dependent Ca^{2+} efflux from the cytoplasm. Likewise, Golgi apparatus restores their Ca^{2+} store via Secretory Pathway Calcium ATPase (SPCA) from extracellular milieu as well as cytoplasm. Lysosomes use transient receptor potential channels (TRPC) for Ca^{2+} transport. Ca^{2+} transport between ER and mitochondria occurs in a highly organized manner through Mitochondrial Associated Membranes (MAMS). IP3 receptor (IP3R) mediated Ca2 + release from ER is sensed and uptaken by mitochondrial Voltage-Dependent Anion Channel (VDAC) and MCU across mitochondrial OMM and IMM respectively. In the mitochondrial matrix, Ca^{2+} plays a major role in cellular metabolism and oxidative phosphorylation to generate ATP required for innumerable cellular processes. However, some other transporters or modes are known to transport Ca^{2+} into mitochondria like uncoupling proteins 2 and 3 (UCP2 and UCP3), leucine zipper-EF-hand-containing transmembrane protein1 (LETM1) and rapid uptake mode (RaM). To overcome the increase in mitochondrial calcium concentration, efflux occurs through the Na+/Ca2+/Li + exchanger (NCLX) across the mitochondrial membrane.

Unchecked Ca^{2+} overload in mitochondria leads to loss of mitochondrial membrane potential (MMP), the opening of mitochondrial permeability Transition Pore (mPTP) and release of apoptotic stimuli. Cytosolic Ca^{2+} returns to its basal level by efflux through Na+/Ca^{2+}exchangers (NCX) and Plasma Membrane Calcium ATPase (PMCA) pump. The range of Ca^{2+} concentrations (from resting to stimulated) in different cellular compartments are indicated in color-coded gradients. Abbreviations: IP3: Inositol 1, 4, 5 Triphosphate; MCU: mitochondrial Calcium Uniporter; OMM: Outer Mitochondrial Membrane; IMM: Inner Mitochondrial Membrane; ATP: Adenosine Triphosphate.

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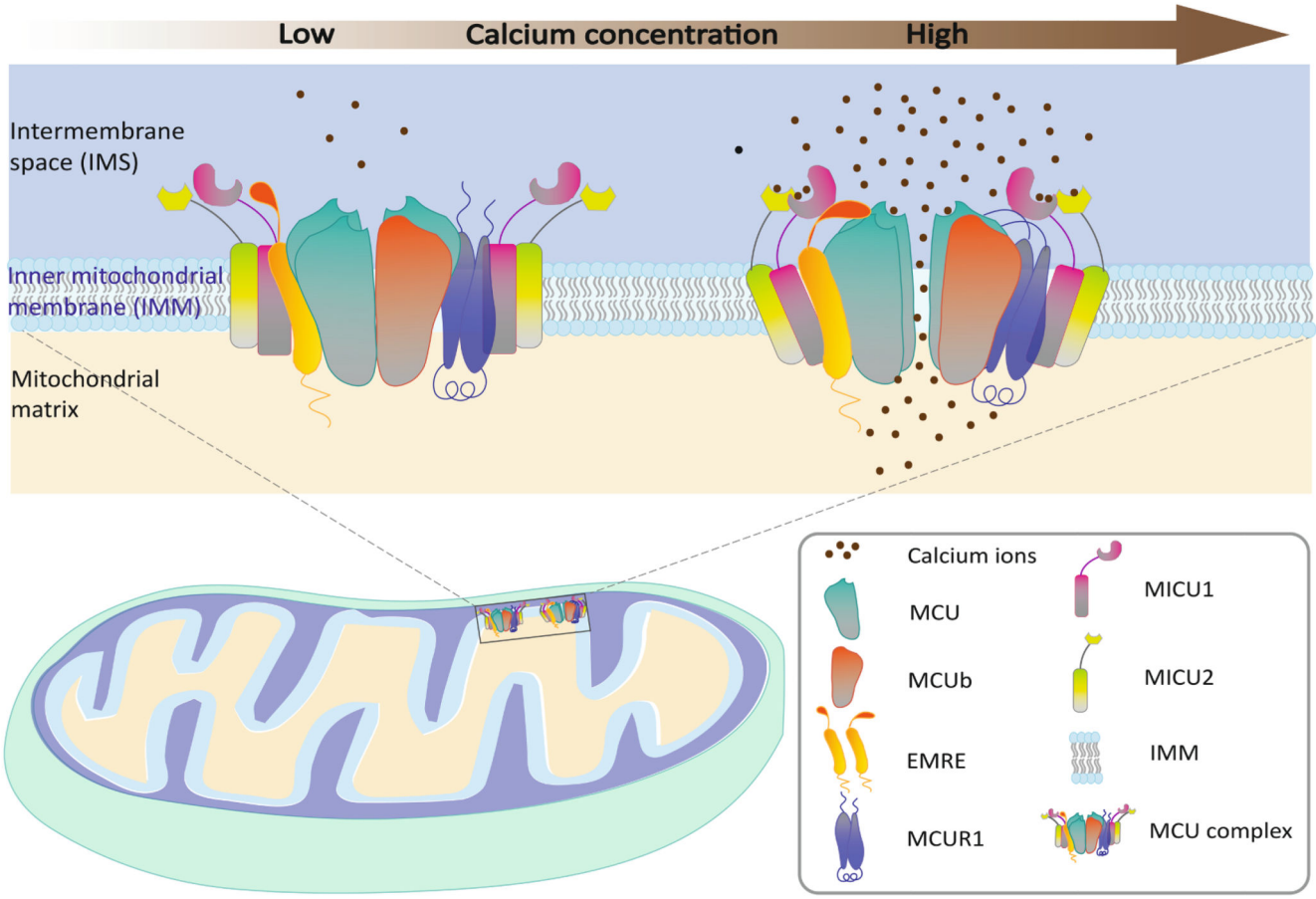

Fig. 2. Schematic diagram of Calcium transport through MCU complex.

Calcium influx mainly occurs via a multiprotein dynamic complex known as MCU in the inner mitochondrial membrane. It is composed of the central pore-forming subunits MCU, the dominant-negative regulator MCUb and the other regulatory subunits MICU1, MICU2, EMRE and MCUR1. At resting conditions (low level of cytosolic Ca^{2+}), MICU1 and MICU2 act as gatekeepers for Ca^{2+} transport and limit calcium passage limiting Ca^{2+} passage through MCU (Left Panel). When the cellular Ca^{2+} signaling is activated leading to an increase in cytosolic Ca^{2+}, MICU1 senses the increase in Ca^{2+} concentration resulting in the change of conformation and heterodimer formation with MICU2. Then MCUR1 establishes the connection between MCU and EMRE to assemble the MCU complex in an open conformation allowing the Ca^{2+} entry through the channel (Right panel).

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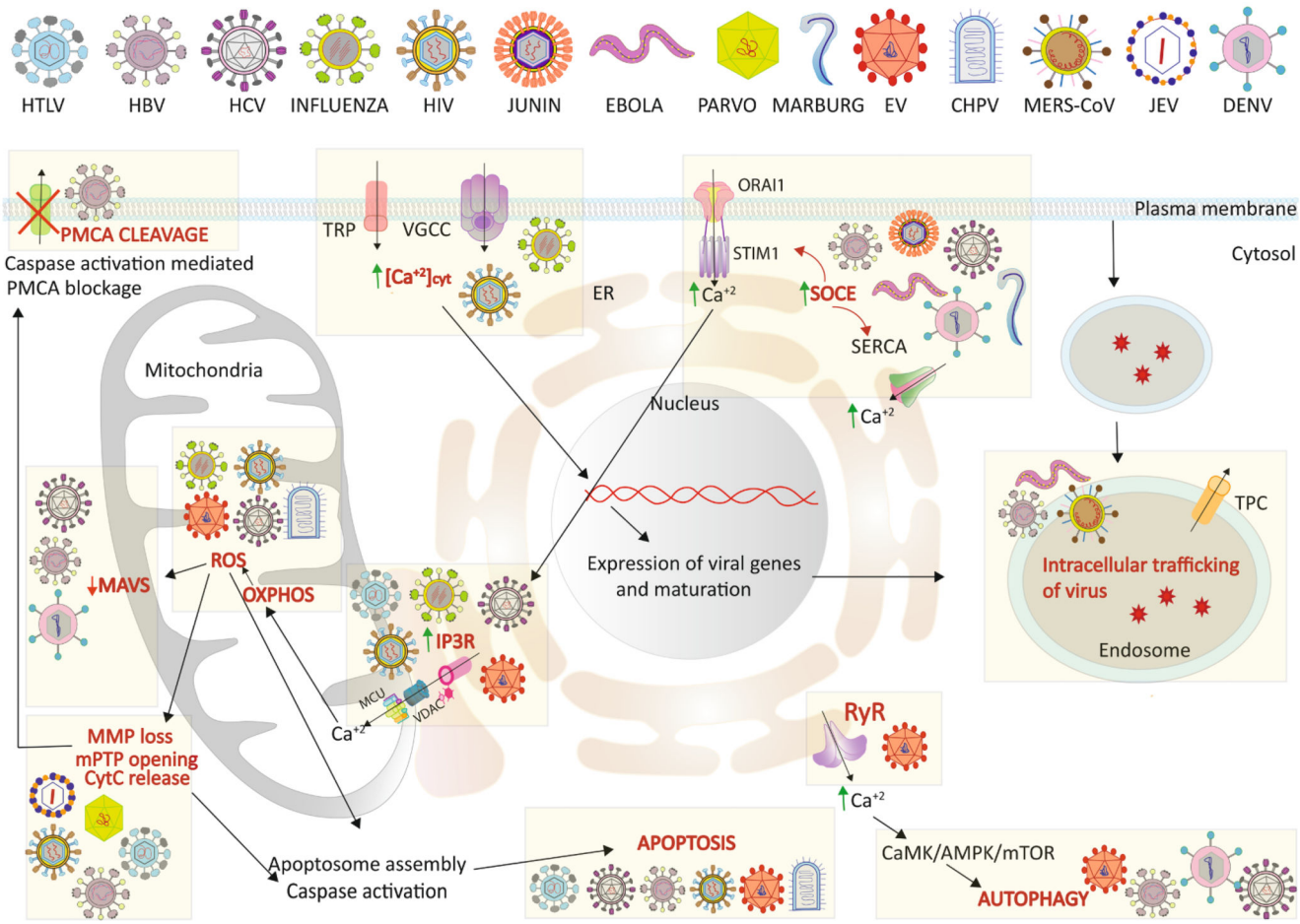

Fig. 3. Model depicting the influence of viral infections on cellular calcium signaling.

Viruses hijack and alter host cellular Ca^{2+} signaling and metabolic pathways to accelerate their replication inside host cells. Certain viruses are known to induce intracellular Ca^{2+} concentrations via Ca^{2+} uptake through different channels like VGCC, TRP. Some of them also activate SOCE channels (STIM1-ORAI1 mediated or through SERCA pump) to enhance uptake by cellular Ca^{2+} stores like ER. IP3R mediated ER-mitochondrial Ca^{2+} transport is also induced in certain viral infections to induce mitochondrial OXPHOS to meet the energy needed for viral replication. Enhanced OXPHOS leads to ROS accumulation that can trigger MMP loss, mPTP opening, Cyt C release and ultimately caspase activation. Caspase activation can block Ca^{2+} efflux via PMCA cleavage altering intracellular Ca^{2+} homeostasis. Increased ROS inhibits MAVS signaling and diminishes cellular innate immune response against viruses. High cytosolic Ca^{2+} can activate PyK2/FAK mediated p53 phosphorylation that in turn enhances specific expression and maturation of viral proteins. A high Ca^{2+} level also helps in the endosomal trafficking of viral particles. Some viruses induce CaMK/AMPK/mTOR mediated autophagy in response to increased cytosolic Ca^{2+}. Viruses inducing these specific events are indicated in the figure appropriately. Please refer to the text for details. Abbreviations: $[Ca^{2+}]_{cyt}$: Cytosolic Calcium; SOCE: Store Operated Calcium Entry; VGCC: Voltage-Gated Calcium Channel; OXPHOS: Oxidative Phosphorylation; ROS: Reactive oxygen species; Cyt C: Cytochrome

C; MAVS: Mitochondrial Antiviral Signaling protein; PyK2: Protein Tyrosine Kinase2; FAK: Focal Adhesion Kinase; CaMK: Ca^{2+}/Calmodulin-dependent protein kinase; AMPK: 5′ AMP-activated protein kinase; mTOR; HTLV: Human T-lymphotropic virus; HIV: Human Immune deficiency virus; HBV: Hepatitis B virus; HCV: Hepatitis C Virus; EV: Entero Virus; CHPV: Chandipura Virus; MERS-CoV: Middle East Respiratory Syndrome Corona Virus; JEV: Japanese Encephalitis Virus; DENV: Dengue Virus.

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Table 1

Role of viruses/viral proteins on Ca^{2+} homeostasis.

Virus	Protein	Cytobiological consequences on Ca^{2+} signaling	Refs.
HIV-1	Nef	Activates T cell Receptors via NFAT activation.Enhances viral infectivity.	(Simmons et al., 2001) (Chami et al., 2006)
	Vpr	Interacts with cellular Ca^{2+} regulators.Induces mitochondrial Ca^{2+} leakage through membrane permeabilization.	(Jacotot et al., 2001, 2000)
	Tat	Induces Ca^{2+} dependent apoptosis	(Kruman et al., 1998)
	gp120	Increases $[Ca^{2+}]_{cyt}$ that leads to increased ROS accumulation	(Haughey and Mattson, 2002)
	Env	Mediates Ca^{2+} dependent viral fusion	(Zaitseva et al., 2017)
HTLV-1	$pI2^{I}$	Increases Ca^{2+} outflow from ER via binding to calreticulin and calnexin.Enhances viral infection through Ca^{2+} dependent activation of transcriptional co-activator p300.	(Ding et al., 2001) (Nair et al., 2006)
	$pI3^{II}$	Affects mitochondrial Ca^{2+} permeability across IMMIncreases the sensitivity of cells to apoptosis.	(D'Agostino et al., 2002) (D'Agostino et al., 2005)
HCV	Core	Decreases $[Ca^{2+}]_{er}$, induces apoptosis via Bax-mediated mitochondrial membrane depolarization.Stimulates ER Ca^{2+} efflux to mitochondria through MCU activation.	(Benali-Furet et al., 2005; John et al., 1998)(Ivanov et al., 2015; Li et al., 2007)
	NS5A	Increases $[Ca^{2+}]_{mt}$ and ROS production and affects transmembrane potential.	(Gong et al., 2001)
		Activates Ca^{2+} -dependent degradation of NFκB inhibitory subunit Iκβα.	(Waris et al., 2003)
	p7	Allows Ca^{2+} -flow from ER by forming ion channels in the cellular membrane	(Griffin et al., 2003)
Poliovirus	Viral particle	Accumulates $Ca+^{2}$ in mitochondria that leads to mitochondrial dysfunction and apoptosis.	(Brisac et al., 2010)
Coxsackie virus B3	2B	Increases $[Ca^{2+}]_{cyt}$ by rigorous Ca^{2+} outflow from ER.	(Peischard et al., 2019)
	3C	Promotes mitochondrial Ca^{2+}mediated apoptosis through cleavage of procaspase 8.	(Peischard et al., 2019)
	2A	Along with 3C, it destabilizes cellular homeostasis by increased expression of Bax, p53 and decreased expression of Bcl2 leading to cell death	(Peischard et al., 2019)
	Viral particle	Disturbs mitochondrial homeostasis. Activates the AMPK/MEK/ERK and Ras/Raf/MEK/ERK signaling pathways to induce autophagy in host cells.	(Xin et al., 2015)
Rabies virus	Viral particle	Hampers Ca^{2+} homeostasis and GABAergic neurotransmission by loss of host proteins calbindin-D-28 k and elevation of m-calpin respectively.	(Schwaller et al., 2002; Torres-Fernández et al., 2005; Ubol et al., 2005)
Influenza virus	Viral particle	Targets Cav1.2 channel for binding and entry into host cells.	(Fujioka et al., 2018)
	M2	Regulates ROS dependent Mitochondrial Antiviral Signaling (MAVS)	(Wang et al., 2019)
Ebola virus	Viralparticle	Affects TPCs to control the movement of endosome-containing virus particles.STIM1/ORAI1-mediated Ca^{2+} signal critical for their budding from host cells	(Han et al., 2015; Kintzer and Stroud, 2016; Sakurai et al., 2015)
Rotavirus	NSP4	Decreases $[Ca^{2+}]_{er}$ and increases $[Ca^{2+}]_{cyt}$ through PLC activation and IP3 production.	(Dong et al., 1997; Tian et al., 1995)
Chandipura virus	Viral particle	Affects intracellular Ca^{2+} signaling mediated by angiotensin II.Causes neuronal apoptosis through FasL-FADD pathway.	(Verma et al., 2018)
HBV	HBx	Activates mitochondrial PTP opening to release mitochondrial Ca^{2+} to cytoplasm and activates Ca^{2+} ATPase to accumulate Ca^{2+} in ER that ultimately releases through IP_3R, thus, results in increased $[Ca^{2+}]_{cyt}$.	(Xia et al., 2006)(Bouchard et al., 2006)

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Virus	Protein	Cytobiological consequences on Ca^{2+} signaling	Refs.
		Enhances viral replication through activation of proline-rich tyrosine kinase 2 (Pyk2) and Focal Adhesion Kinase (FAK).	
HHV-8	K1	Increases prolonged intracellular Ca^{2+} concentration through a phosphorylation cascade of downstream elements.	(Lee et al., 2005)
	K7	Elevates $[Ca^{2+}]_{cyt}$ by interacting with CAML protein of ER and activation of CCE pathway.	(Feng et al., 2002)
HSV		Increased $[Ca^{2+}]_{cyt}$ results in FAK phosphorylation required for actin cytoskeleton reorganization and nuclear trafficking of the internalized virus. Enhances proinflammatory response through activation of NFkB.Targets T-type Ca^{2+} channels, downregulates VGCC and alters sensory neurons to transmit pain information.	(Chami et al., 2006; Chen et al., 2019b; Cheshenko et al., 2003; Mogensen et al., 2003; Zhang et al., 2019a, 2017)
Epstein-Barr virus	LMP1	Reactivates EBV in a calcium-dependent manner inducing a Ca^{2+}/calmodulin dependent protein kinase type IV/Gr (CaMKIV/Gr).	(Chatila et al., 1997; Mosialos et al., 1994)
	LMP2A	Binds cellular phospho-tyrosine kinases (PTKs), prevent calcium mobilization and acts as a negative regulator of calcium-signaling.	(Fruehling and Longnecker, 1997; Miller et al., 1994, 1993)
HPV	E6	Interacts with E6BP, a Ca^{2+} binding protein of ER.	(Chen et al., 1995; Weis et al., 1994)
	E7	Allows virus-induced oncogenic activity.	(Tugizov et al., 2005)
HCMV	UL37X1	Activates STIM1/ORAI1 mediated calcium influx.	(Chen et al., 2019b)
Dengue virus	Viral particle	Activates SOC channels altering cellular Ca^{2+} homeostasis via STIM1/ORAI1 interaction.	(Cheshenko et al., 2007; Dionicio et al., 2018)