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Cyclophilin A: A Key Factor in Virus Replication and Potential Target for Anti-viral Therapy

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Abstract
Cyclophilin A (CypA) is a key member of immunophilins that has peptidyl-prolyl cis/trans isomerase (PPIase) activity. Besides acting as a cellular receptor for immunosuppressive drug cyclosporine A (CsA), CypA is involved in various cellular activities. CypA has an important role in viral infection which either facilitates or inhibits their replication. Inhibition of CypA via inhibitors is useful for overcoming several viral infections, indicating that CypA is an attractive target for anti-viral therapy. Collectively, these facts demonstrate the critical roles of CypA in mediating or inhibiting viral infections, suggesting that CypA can be an attractive cellular target for the development of anti-viral therapy.

Introduction
Cyclophilins (Cyps) comprise the family of peptidyl-prolyl isomerases (PPIases), which ubiquitously express in every prokaryotic as well as eukaryotic cells (Wang and Heitman 2005; Davis et al., 2010) and localize in every major cellular compartment (Pemberton and Kay, 2005). All the members of this family have a common conserved domain of peptidyl-prolyl cis-trans isomerases (PPIase) bordered by a unique domain, which functionally sequesters each member (Göthel and Marahiel, 1999; Kaul et al., 2009). The PPIase is an enzymatic process involved in the inter conversion between the *cis* and *trans* isomers of the N-terminal amide bond of the amino acid proline (Lu et al., 2007; Davis et al., 2010), which particularly induces the folding process of proteins (Kern et al., 1994). Cyps are categorized by having a high binding affinity to immunosuppressive drug cyclosporine A (CsA), a cyclic peptide derived from a fungus *Tolypocladium inflatum* (Göthel and Marahiel, 1999). Cyps have been ascribed multiple functions in a variety of organisms and cellular systems. These functions include association in cell signaling pathways such as Itk (Brazin 2002), gene regulation (Göthel and Marahiel, 1999), mitochondrial activity (Liu et al., 1991), nucleolytically genome degradation (Montague 1997), protein folding and trafficking (Schmid et al., 1993), apoptosis (Lin and Lechleiter 2002), and virus infection (Chatterji et al., 2010; Yan et al., 2015).

CypA, a key member of the immunophilins, is one of the most abundant proteins (approximately 0.1-0.4% of the total cellular protein) in the cytoplasm (Saphire et al., 1999; Fischer and Aumüller 2003). It is involved in cellular functions like immunomodulation, cell signaling, transcriptional regulation, protein folding and trafficking (Liao et al, 2007; Nigro et al., 2013). CypA was initially discovered as an intracellular receptor for the immunosuppressive drug cyclosporine (Cs).

The CypA-Cs complex binds and inhibits the protein phosphatase calcineurin, preventing T-cell activation in mammals (Liu et al., 1991, 1992). CypA acts as pro-inflammatory mediator, which stimulates inflammatory responses through CD147 (the chief cell receptor for CypA) (Yurchenko et al., 2006). It also exerts chemotactic activity for neutrophils (Wang et al., 2010), and human, mouse and fish leukocytes in vitro (Yeh et al., 2013; Gwinn et al 2014; Dong et al., 2015; Obchoei et al., 2015). In addition, CypA regulates the amplitude and duration of different cellular process by functioning as molecular signaling switches (Lu, et al., 2007). CypA has been found to be involved in nuclear translocation and activation of ERK1/2 and apoptosis-inducing factor (AIF) (Zhu, et al., 2007; Pan et al., 2008). It can inhibit IL-4 induction by Itk (Colgan et al., 2004) and regulates the RA-induced neuronal differentiation (Song et al., 2004). Moreover, CypA may also facilitate the interleukin-6 (IL-6)-induced signal transducer and activation of transcription 3 (Stat3) tyrosine phosphorylation and nuclear translocation (Bauer et al., 2009), and can strongly associate and activate NF-kB *in vitro* and *in vivo* (Obchoei et al., 2009; Sun, et al. 2014).

CypA works against immune-mediated injuries like acetaminophen toxicity (reviewed in Naoumov, 2014). In Rheumatoid arthritis (RA) patients, it can induce the production of inflammatory cytokines (IL-1β, TNF-α, IL-8, MMP-2, MMP-9), monocyte chemoattractant protein-1 (MCP-1) and cartilage destruction (Kim et al., 2005; Wang et al., 2010). Similarly, stably expressed CypA in the hepatocellular carcinoma SK-Hep1 cell line can up-regulate the expression of many cytokine-related genes such as IL-8, IL-6, IL-1β, CXCL1, CXCL3 and CXCL2, which contribute in tumor cell growth (Chen et al., 2008). In addition, secreted CypA increases the proliferation of pancreatic and lung cancer cells by activation of p38-MAPK and extracellular signal regulated kinases 1/2 (ERK1/2) pathways (Li et al., 2006). CypA is involved in cancer and cardiovascular disease (Jin et al., 2000; Liao et al., 2007). During atherosclerosis, CypA has a pro-inflammatory effect on endothelial cells (EC) and shows exacerbation of oxidative stress and inflammation in human (Jin et al., 2004; Satoh et al., 2009). CypA also functions againsts lipopolysaccharides (LPS) and bacterial challenge (Qiu et al., 2009; Song et al., 2009).

Besides the diverse functions from normal cell physiology (Freskgard et al., 1992; Colgan et al., 2004) to numerous diseases (Obchoei et al., 2009), CypA is widely involved in viral replications (Chatterji et al., 2009). Zhou et al. (2012) showed that CypA is associated in the life cycle of several viruses, but recent comprehensive reports regarding the current advances in the role of CypA during viral infection is lacking. Therefore, the aim of the current review is to discuss all the known roles of CypA during virus replication, which either facilitate or inhibit the replication process. In addition, the advances in the control of viral infections through inhibition of CypA are discussed in detail. This review would help in the understanding of the association between CypA and viral infections, and would provide information to aid the discovery and selec-

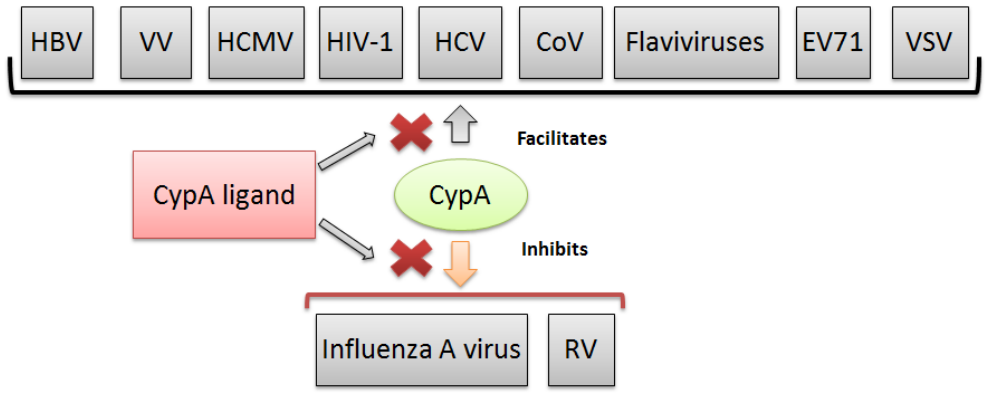

Figure 1. CypA facilitates or inhibits the replication of viruses. Therefore, CypA is an attractive target for anti-viral therapy.

tion of host targetd therapies for viral disease (Figure 1).

CypA role in facilitating of viral replication

CypA facilitates viral infection (Chatterji et al., 2009; Liu et al., 2012), either by interaction with viral proteins or facilitating other cellular factors (Hsp90) essential for their replication (Okamoto et al., 2006; Stone et al., 2007; Bienkowska-Haba et al., 2012). CypA plays a critical role in the propagation of Hepatitis B virus (HBV), vaccinia virus (VV), Humanimiunodefiency virus type 1 (HIV-1), hepatitis C virus (HCV), coronaviruses (CoV) and vesicular stomatitis virus (VSV) (reviewed in Zhou, et al., 2012). In addition, CypA can also facilitate the replication of Human cytomegalovirus (HCMV) (Keyes et al., 2012), flaviviruses (Qing et al., 2009) and Enterovirus (EV71) (Qing et al., 2014). CypA associate and facilitate replications of DNA, positive strand RNA and negative strand RNA viruses in a similar fashion and are shown in detail respectively (Table 1).

Hepatitis B Virus

CypA facilitates the replication process of HBV, a member of the family Hepadnaviridae (littlejohn et al., 2016) and the smallest human DNA virus (Dandri et al., 2012). HBV-RNA transcribes all structural and nonstructural viral proteins while replicating in the cytoplasm (Dandri et al., 2012). HBV has an abundant small surface antigens (SHBs) protein in virion and subviral particles with which CypA interacts and helps in replication (Tian et al., 2010). CypA level is decreased in the hepatocytes of transgenic mice expressing HBV surface antigen (HBsAg) but significantly increased in their sera. The reduction of CypA level in HBsAg expressing hepatocytes may also affect protein unfolding and facilitate HBV infections similar to HIV (Zhao et al., 2007). HBV SHBs initiates secretion of CypA in human hepatoma cell lines but not in cultural medium. SHBs expression inoculation into C57BL/6J mice exhibits increased serum ALT/AST, CypA level and inflammatory cells influx ratio. However its mutant SHBs fails to trigger CypA secretion. Chronic hepatitis B infection elevates the level of serum CypA compared to healthy individuals (Tian et al., 2010). The knockdown of CYPA and its enzymatic activity reduces the secreted of HBV-DNA by 80% in HepG2215, HepaRG and HuH-7 cells. In addition, it can block the secretion of HBsAg (envelope protein) and binds them inside the cells (Phillips et al., 2015) as SHBs and CypA are secreted together via the vesicular secretion pathway from hepatocytes (Patient et al., 2007; Tian et al., 2010).

Vaccinia virus

Vaccinia virus (VV) is a key member of Poxviridae family (Damaso and Moussatche 1998). Its double stranded DNA replicates solely in the cytoplasm of infected cells producing DNA and protein entities in the form of virosomes or viral factories (Joklik and Becker 1964), where CypA get-together and involves in its replication cycle (Damaso, and Moussatche 1998). Initially, incorporation of CypA into vaccinia virus particles exhibits increased stability and extended half-life, leading to an unchanged accumulation of CypA in VV-infected cells. But at late time of in-

Table 1. CypA interacts with viral proteins and facilitates the replication of viruses.

Serial No.	Virus species	Genome structure	Function of CypA	Reference
1	Hepatitis B virus (HBV)	Partial double stranded DNA	Interacts with SHBs and helps in replication	Tian et al., 2010.
2	Vaccinia virus (VV)	Double stranded DNA	Encapsulated into the space between the core protein A12L and the IMV envelope,	Castro et al., 2003
3	Human cytomegalovirus (HCMV)	Doublestranded DNA	Helps in expression of IE proteins and virus reactivation (latency)	Keyes et al., 2012
4	Humanimiunodefiency virus type 1 (HIV-1)	Retrovirus	Interacts with N-terminal domain of CA protein	Shah et al., 2013
5	Hepatitis C virus (HCV)	Positive stranded RNA	Interacts with either NS5B or NS5A and supports viral replication	Chatterji et al., 2009
6	Coronaviruses (CoV)	Positive stranded RNA	Binds with nucleocapsid (N) protein of SARS-CoV and helps in replication	Chen et al., 2005
7	Flaviviruses	Positive stranded RNA	Binds to the genomic RNA and NS5 protein to regulate replication	Qing et al., 2009
8	Enterovirus (EV71)	Positive stranded RNA	Interacts to H-I loop of VP1 protein and regulates the uncoating process of EV71 entry	Qing et al., 2014
9	Vesicular stomatitis virus (VSV)	Negative stranded RNA	Conspires with the nucleocapsid (N) protein and helps in folding	Boss et al., 2003

fection, cellular CypA fading-out, which indicates its intense need for VV infection (Moss, 1968; Castro et al., 2003). In the cytoplasm, CypA interacts with the viral factories/virosomes during morphogenesis by the help of viral post-replicative proteins at late time of infection. CypA encapsulates into the virus particle and get access to the space between the core protein A12L and the IMV envelope, as shown by purified viroins (Castro et al., 2003). In mock-infected cells, CypA is uniformly distributed throughout the cell cytoplasm, while CypA evidently changes its intracellular organization at the late stage of infection ending with full relocation to the virosomes. (Ryffel et al., 1991; Le Hir et al., 1995).

Humancytomagalo virus

Humancytomagalo virus (HCMV) and murine cytomegalovirus (MCMV) are the members of family herpesvirus, with linear double stranded DNA genome (Fields et al., 2001), experiencing critical affects from CypA while replicating in the host (Kawasaki et al. 2007). HCMV is a key member of the subfamily Betaherpesvirinae. Initially, HCMV shows limited replication, while reactivation upon immune suppression of the host. The mechanisms of HCMV latency are not fully understood in terms of viral gene expression and the cellular factors involved. However, CypA role is established in the regulation of MCMV. Silencing CypA in neural stem and progenitor cells (NSPCs) reduces virus yields by 50%, although MCMV replication in fibroblasts is unaffected (Kawasaki et al., 2007). Similarly, silencing CypA in human foreskin fibroblast (HF) through siRNA decreases the viral production by delaying expression of (IE) proteins, decreasing viral DNA loads and reducing titers. Additionally, CypA silencing in THP-1 cells during pre- and post-differentiation states, inhibits the expression of immediate-early IE protein and virus reactivation. Hence CypA is an important cellular factor for HCMV production and reactivation in HF and THP-1 cells respectively (Keyes et al., 2012).

Human immunodeficiency virus type 1

HIV-1 is a member of family Retroviridae with positive-stranded RNA genome. After integration of its genome into the host cell, the encoded protease cleaves viral Gag polyprotein into capsid (CA), matrix (MA) and nucleocapsid (NC) proteins (Ganser-Pornillos et al., 2008). CA protein has a proline-rich stretch of the single exposed loop consisting of Pro85 to Pro93. The Gly89 and Pro90 amino acids are the binding sites for catalytic domain of CypA (Gamble et al., 1996), which are easily accessible to CypA in the cytosol of the newly infected cell. In the late phase of infection, CypA interacts with the N-terminal domain of CA and catalyzes the isomerization of the Gly89\Pro90 bond, thus acting as a chaperone during its replication. This CA-CypA complex positively affects the dimerization of CA and helps in viral replication (Shah et al., 2013). The loaded CypA over HIV-CA remains exposed till getting attached to the target cell surface via heparin, as CypA has a domain equipped with residues that has a capacity to bind with heparin. This attachment is belived as the primery phase of HIV-1 attachment (Saphire et al., 1999), as the bonded CypA entrance triggeres reverse transcription in the host cell (Schaller et al., 2011). CypA get together at very early stages because anti-CypA antibodies inhibit viral uptake

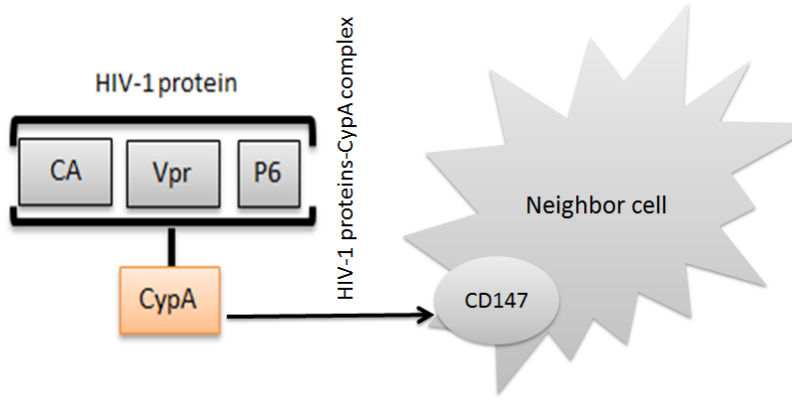

Figure 2. CypA gets together with CA, Vpr or P6 proteins of HIV-1 and catalyzes the isomerization of the Gly\Pro bond. It can also regulate HIV-1 attachment to host cells or facilitates the phosphorylation of HIV-1 matrix protein by attaching to the target cell through CD147.

and thus disrupt HIV-1 infection (Sherry et al., 1998). During this early replication assembly, the bonded CypA to a proline-rich site of CA facilitaes its incorporation, while inhibiting CypA encapsidation yields in noninfectious HIV virioins (Colgan et al., 1996). CypA interaction with newly synthesized HIV-1 CA is mandatory for HIV-1 infection (Hatziioannou et al., 2005), as CypA is equally essential for HIV-1 infection and virions formation (Goldstone et al. 2010) (Figure 2).

In addition to CA binding, CypA can facilitate HIV-1 proliferation by interaction with extracellular CD147-the main receptor for CypA on the cell membrane of human leukocytes. CypA- CD147 complex either regulates HIV-1 attachment to host cells or facilitates the phosphorylation of HIV-1 matrix protein, which subsequently liberates the reverse transcriptase complex into cytoplasm during initial stage of HIV-1 infection (Pushkarsky et al. 2001). CypA also interacts with other HIV-1 proteins like Vpr and p6 to propagate its infection (Colgan et al., 1996; Bruns et al., 2003). Studies reported that CypA does not interfere with HIV-1 as an uncoating factor by affecting HIV-1 assembly, maturation or core stability (Wiegers et al., 1999). Recent research reported that CypA stabilizes the HIV-1 capsid and antagonizes HIV-1 uncoating in vitro, demonstrating the versatile functions of CypA in HIV-1 infection (Shah et al. 2013) (Figure 2). However, the exact mechanism by which CypA promotes HIV-1 replication remains unknown (Shah and Aiken 2014).

A92E and P90A mutants of CA can't make CA-CypA interaction *in vitro* in HeLa cells and in Jurkat T lymphocytes, respectively (Li, et al., 2009). In addition, manipulation in CypA encoding site of PPIA gene makes it susceptible to HIV-1 infection (Rits et al., 2008), although wild type CypA are resistant to HIV-1 infection (Neagu et al., 2009). Mutation in the CypA binding residues (G89 or P90) of CA can't interact with CypA, thus prevent CypA incorporation into virions (Schaller et al., 2011; Shah et al., 2013). The decrease in the CA stability due to mutants suggests that it can modulate capsid assembly during infection (Cortines et al., 2015). H126Q, a mutant CypA interacts with HIV-1 virion in an attenuated fashion compared to wild type (Kaul et al., 2009). CypA also acts as inhibitor for CsA-resistant mutants of HIV-1 in certain cells (Hatziioannou et al., 2005). Moreover, in Old World monkey cells, CypA by interacting with CA inhibits HIV-1 infection by TRIM5a (Stremlau et al., 2006). This is probably due to the notion that CypA could affect HIV-1 capability of unbinding thereof by modulating HIV-1 capsid departure (Li et al., 2009). The response of human cells to enhancement and restriction of HIV-1 are paradoxically reported, however the presence of an unknown CypA-dependent restriction factor is considered responsible for the process in cell types that are non-permissive to CsA-dependent mutants (Shah and Aiken 2014). Recently, human MxB protein is reported to be involved in CypA-dependent HIV-1 inhibition (Goujon 2013; Liu et al. 2013). However to date, it is established that CypA-CA interaction helps HIV-1 to infect human cells.

Hepatitis C virus

Hepatitis C virus (HCV), is a key member of the family Flaviviridae, having positive-strand RNA genome encoding a single polyprotein (Lindenbach, and CRice, 2005). HCV-RNA usually replicates using intracellular membranes (Salonen and Kaariainen, 2005) where cellular proteins regulate its replication either by interaction with viral proteins or by essential metabolic pathways modulation (Okamoto et al., 2006; Stone et al., 2007). CypA, being a cytosolic protein, plays a prominent role in HCV life cycle (Chatterji et al., 2009) and acts as co-factor for HCV infection in vitro (Kaul et al. 2009; Ciesek et al., 2009). CypA via its enzymatic/hydrophobic pocket either promotes HCV replication by enhancing the affinity of HCV polymerase nonstructural 5B (NS5B) for viral RNA (Chatterji et al., 2009) or combines with various HCV nonstructural 5A (NS5A) protein, to form CypA-NS5A complex (Chatterji et al., 2010; Dorner et al., 2013) consequently mediating NS5A-domain II to facilitate RNA replication promotes viral protein folding and regulates poly protein processing (Foster et al., 2011). This phenomenon is conserved in all HCV genotypes (Chatterji et al., 2010). Like NS5A and NS5B, CypA interacts with HCV NS2 (Ciesek et al., 2009) and propagates HCV replication in similar fashion (Figure 3). CypA fails to affect domain II (D316E and D316E/Y317N) mutants of HCV (Foster et al., 2011), but can bind with HCV-NS5A mutant (Chatterji et al., 2010). CypA devoid of its isomerase activity (H126Q), failed to bind NS5A or NS5B suggesting the importance of CypA isomerase port (Chatterji et al., 2010). In contrast, Chatterji et al. (2010) argue against a model where CypA regulates HCV replication by employing NS5B or NS5A into the replication

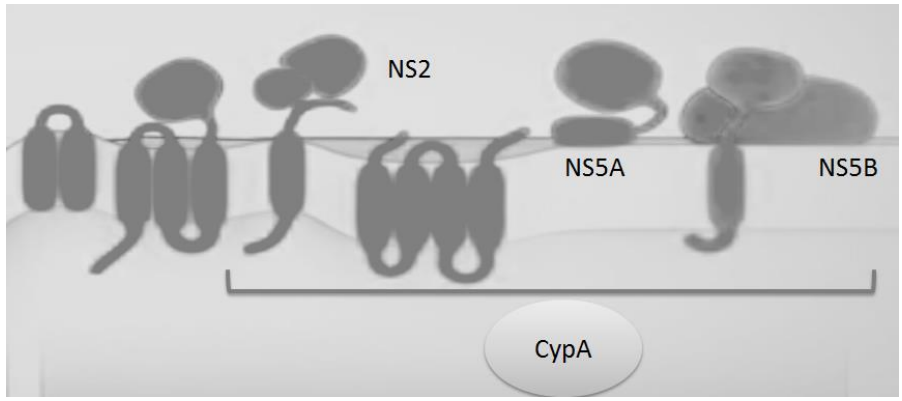

Figure 3. CypA can combines and enhancing the affinity of HCV polymerase NS5B for viral RNA replication. It can form a complex with HCV nonstructural protein NS5A and NS2 which facilitates RNA replication promotes viral protein folding and regulates poly protein processing.

complex. They stated that CypA get access to protease-resistant compartment adjacent to HCV replication site through its isomerase pocket and this access is not facilitated by HCV. Therefore, decrease in CypA level in replication complex does not affect NS5A and NS5B association in replication complex.

Several other studies confirmed that CypA peptidyl-prolyl isomerase activity is critical for HCV replication (Kaul et al., 2009; Chatterji et al., 2009; Dorner et al., 2013) while isomerase-deficient CypA are unable to support HCV replication (Chatterji et al., 2009). H126Q, a CypA mutant interacts with HCV virion in an attenuated fashion compared to wild type (Kaul et al., 2009). Mutantions at the hydrophobic pocket of CypA (histidine126 and arginine55) makes it unable to support HCV replication, suggesting that HCV consume CypA's isomerase/chaperone activity for replication. It also suggests that CypA catalyzes a *trans* to *cis*- or a *cis* to *trans*-isomerization of a peptidyl-prolyl bond either in a viral or cellular protein crucial for HCV replication (Chatterji et al., 2009). CypA knock-down exhibits significantly decreased HCV-RNA replication in Huh7 cells (Kaul et al., 2009; Chatterji et al., 2010). Up and downregulation of wild type CypA is directly proportional to replication of subgenomic HCV replicons whereas mutant CypA lacks this function (Kaul et al., 2009). Despite the known information, the mechanism of how the peptidylprolyl isomerase activity of CypA regulate HCV replication, and the formation and function of CypA-NS5A/NS5B complex are not fully elucidated. Further studies are required to determine whether CypA acts at several steps of the HCV life cycle, as CypA associates with HCV before budding (Chatterji et al. 2009).

Coronaviruses

CoVs are enveloped and positive-stranded RNA viruses, belongs to family Coronaviridae. The genome of CoVs comprising of spike (S), envelope (E), membrane (M), and nucleocapsid (N) encoding proteins (Guan et al., 2003). Like other viruses, CoVs replicates in host cells by making direct or indirect interaction cellular proteins (Kontoyiannis et al., 2003). Cellular CypA is the vital binding partner with N protein of SARS-CoV (Luo et al., 2004). A study using unbiased yeast-two-hybrid screening discovered that CypA bind to Nsp1 protein of SARS-CoV (Pfefferle et al., 2011) and HCoV-NL63 virus. The nucleocapsid (N) protein of SARS-CoV interacts with CypA, which mediates HAb18G/ CD147 to interact with SARS-CoV N protein, and thus helps in viral replication in 293 cells (Chen et al., 2005). Furthermore, silencing of the cellular CypA through siRNA inhibits the replication of HCoV-NL63 virus in Caco-2 cells, revealing the requirement of CypA for CoV infection (Carbajo-Lozoyaa et al., 2014). By contrast, CypA was observed only on the surface of mature SARS-CoVs, by electronic microscopy. This contradiction was partly explained by another statement that CypA bound to viral proteins in the core can be relocated from the core to the viral surface during maturation of the virus (Saphire et al., 2000). Similarly, Wilde et al. (2011) reported that CypA, which are involved in the replication of other viruses, is not required for SARS-CoV replication in 293/ACE2

cells. Although the accurate molecular mechanism by which CsA inhibits coronavirus replication needs further intense studies, it may be possible that CsA would functionally be involved in the CypA and viral protein hypothesis complex. If this hypothesis is further confirmed, it will pave the way to discover the potential of these host proteins for the development of coronavirus-wide therapies. Taken together all these findings evidenced the role of CypA in the cytologic mechanism of CoV infection and provide a molecular base for further studying and screening of anti-CoV drugs.

Flaviviruses

Flaviviruses, are members of family Flaviviridae having positive-sense-single-stranded RNA genome encode a polyprotein, which produce all the structural and nonstructural proteins under the supervision of viral and cellular proteases (Lindenbach et al., 2007). CypA acts as essential host factor for flaviviruses replication. CypA binds to the genomic RNA and NS5 protein of West Nile Virus (WNV) to regulate its replication, as revealed by biochemical pulldown analyses, but it does not directly interfere with the enzymatic activities of NS5 *in vitro.* The CypA knockdown Huh-7.5 cells shows decrease replication of WNV, dengue virus, and yellow fever virus. This low replication can be enhanced by the addition of wild-type CypA but not by the supply of a mutant CypA (PPIase deficient) (Qing et al., 2009). The CypA involvement in Flaviviruses replication is not fully understood. Therefore, further studies are encouraged to explore its molecular participation.

Enterovirus

Enterovirus (EV71) belongs to the family Picornaviridae with a positive, single-stranded RNA genome. During replication, its RNA encodes four structural proteins (VP1, VP2, VP3, VP4) (Ranganathan et al., 2002; Wang et al., 2012) and two non-structural proteins such as RNA-dependent RNA polymerase and proteases, which catalyzes its own viral proteins (Huang et al., 2014). The capsid proteins VP1 surface has a depression and mostly contains the receptor-binding site for CypA (Rossmann, 1989). CypA directly interacts to H-I loop of the VP1 protein and alters its configuration and thus plays a critical role in the uncoating process of EV71 entry. CypA regulates Enterovirus (EV71) replication by catalyzing its accurate cis-trans reaction, as shown by the Nuclear Magnetic Resonance (NMR) spectroscopy. The knockdown of endogenous CypA through siRNA decreases viral replication (EV71 RNA and VP1 protein) in rhabdomyosarcoma (RD) cells and Huh7.5.1 cells. EV71 infection up-regulates the expression of host cell CypA in the rhabdomyosarcoma (RD) cells (Qing et al., 2014). Proline instead of serine at position S243 of VP1 protein increases the attraction of CypA with EV71 virions. Moreover, H126Q is a mutant form of CypA, which can reduce the binding affinity of CypA and EV71 virions (Qing et al 2014).

V*esicular stomatitis virus*

Vesicular stomatitis virus (VSV), a member of family Rhabdoviridae, is a negative strand RNA virus (Rose and Whitt, 2001). Its mRNA codes for nucleocapsid (N) protein, phosphoprotein (P), the RNA polymerase L protein, matrix (M) and glycoprotein (G). The first 3 viral ribonucleoproteins carry out replication (Banerjee, 1987), while M and G are involved in virus budding and entry, respectively (Lyles et al., 1992; Chong and Rose, 1993). Despite the possession of its own protein, VSV employs several host proteins for replication (Harty et al., 2001). CypA is one of those essential host protein, which VSV employes for efficient replication and infection. CypA is traditionally associated with the N protein of VSV viroins. This is probably to isomerize the proline residues required for proper functional folding of this protein (Boss, et al., 2003), because the encapsidating way to the viral genome is similar to the capsid protein of HIV-1 (Agresta and Carter 1997). CypA is basically required for VSV intracellular primary transcription, forming a complex of CypA with N protein of VSV (Boss, et al., 2003), which is believed to be folded for initiation of replication and is well documented elsewhere (De et al., 1982). The interaction behaviour of CypA with VSV is varying for each sub-type. For example, CypA is obligatory for N protein function of VSV-NJ, than VSV-IND, although it combines with progenies of both serotypes. CypA, devoid of its isomarase activity, decreases VSV-NJ replication, signifying the requirement of enzymatically functional CypA for its replication (Boss, et al., 2003).

The inhibitory role of CypA in viral replication

CypA help in restriction of influenza and rotavirus (RV) replication (reviewed in Zhou, et al. 2012). Studies showed that CypA interacts and represses viral proteins and inhibits influenza and rotavirus infections (Liu et al., 2012; He et al.,

2013) (Table 2). The ways that adapt CypA to restrict virus replication are shown in detail.

Influenza virus

Influenza viruses are negative single-stranded RNA viruses (Wise et al., 2011), and belonging to Orthomyxoviridae family (Palese and Shaw 2007). Matrix protein 1 (M1) is the richest conservative protein that regulates the replication, assembly and budding of the Influenza virus. CypA is reported to integrate with influenza virus (Shaw, et al., 2008) and prevent its replication (Liu et al., 2013). CypA, *in vitro* and *in vivo* interacts with M1 protein and prevent the formation of viral particles and infectivity in the influenza A. The functional middle (M) site of M1 is the binding target for CypA as shown by mutagenesis study. During early infection and influenza viral replication, human CypA prevents the transportation of newly synthesized M1 protein into nucleus and hence exhibits inhibitory activity (Liu, et al., 2009; Liu et al., 2013). The knockdown of CypA through siRNA increases the viral replication while up-regulation of CypA deduces its infectivity. Influenza virus inhibition by CypA is not dependent upon its isomerase activity because CypA R55A mutation could also bind to the M1 protein (Liu et al., 2009). Higher infection of influenza virus in CypA-deficient cells while depleted infection in cells, with endogenous CypA, are revealed in 293T cell line, coupled with the notion that CypA don't affect viral genome replication or transcription and also don't harm the transport of viral mRNA to the nucleus. However, CypA decreases the viral protein expression. CypA can accelerate the degradation of M1 and subsequently delays the Influenza virus to be detected (Liu et al., 2012). Another study reported that Chicken CypA protein binds with M1 protein of influenza virus and prevents its infection in Chicken Embryo Fibroblast (CEF) cells, while over-expression of CypA decreases influenza viral infection (Xu et al., 2010). CypA is upregulated with influenza viral infection in a human gastric carcinoma cell line (AGS) (Liu et al., 2008), while not significantly affected after avian influenza virus infection, which can translocate the virus from cytoplasm to nucleus (Xu et al., 2010). CypA phosphorylation and nuclear translocation can also be induced by ligand stimulation of chemokine receptor CXCR4 (Pan, 2008). Taking together, all the studies suggest that CypA restricts influenza virus replication through accelerating the degradation of the M1 protein, and is inhibitory manipulator protein to influenza virus replication.

Rotavirus

Rotavirus (RV) is a member of the family Reoviridae with nonenveloped capsid (Dennehy, 2005). Its genome contains double-stranded RNA that encodes 6 structural proteins (VP1, 2, 3, 4, 6, 7) and six nonstructural proteins (NSP1-6) (Jayaram, et al., 2004). During early infection, the newly synthesized viral NSP1 protein activates PI3K/Akt pathway in host cells (Bagchi et al., 2010), which facilitate the expression of hypoxia-inducible factor-1α (HIF-1α) (Jiao and Nan 2011), that can significantly facilitates CypA transcription (Choi et al., 2007). CypA gets temporal up-regulation upon RV infection and decreases host cells susceptibility to Human rotavirus (HRV) infection in MA104 cells. CypA associates with the viroplasm and interacts with structural protein VP2 of HRV and inhibits HRV replication by pulling down viral proteins expression. Silencing endogenous CypA facilitates both viral gene and protein expressions indicating that CypA can inhibit its expression (He et al., 2013). Another report evidenced that CypA prevents RV replication through mediating host cellular IFN-b production, which is independent of its PPIase activity. The transfection and overexpression of CypA facilitates IFN-b production, which subsequently inhibits RV replication. In contrast, knockdown of CypA through siRNA induces RV replication due to decrease of IFN-b production in MA104, HEK293 and Caco-2 cell lines (He et al., 2012). Collectively, these reports enclosed CypA acting as viral inhibitor and suggest that it would help in discovering anti-viral agents.

Table 2. The inhibitory mechanisms of CypA in replication and life cycle of viruses.

Serial No.	Virus species	Genome structure	Function of CypA	Reference
1	Influenza virus	Negative stranded RNA	Interacts with M1 protein and prevents the formation and the infectivity	Liu et al., 2013
2	Rotavirus (RV)	Double stranded RNA	Interacts with viral NSP and VP2 of HRV and inhibits the replication by pulling down viral protein expression	He et al., 2012, 2013

CypA inhibition: a potential therapeutic uses

In the last few decades, substantial studies have focused on the development of CypA inhibitors since CypA is associated with the regulation of disease and viral infections (Sokolskaja et al., 2010; Yang et al., 2015). The development of host CypA inhibitors has been regarded as an alternative approach for viral infection because it is selective, effective and safe (Yang et al., 2015). For example, in HepG2215, HepaRG and HuH-7 cells, alisporivir decreases the intracellular HBV DNA level probably by breaking its contact with CypA. The combination of alisporivir and telbivudine has greater antiviral effects than the separated ones (Phillips et al., 2015). Anti-CD147 antibody and CsA can disrupt the chemotactic activity of CypA, decrease the serum ALT/AST level and thus preventing HBV replication (Tian et al., 2010). Consequently, CypA is associated as an effective therapeutic target for controlling HBV infection (Table 3).

Cyclosporin, a CypA inhibitor, can prevent VV replication (particularly VV morphogenesis) in BSC-40 cells (Damaso, and Moussatche 1998) banning CypA reallocation to viral DNA factories. The blocking of VV replication by CsA and their analogs depends upon their binding ability with CypA, revealing the importance of CypA during VV replication (Damaso, and Moussatche 1998). Impeding CypA through CsA is also effective in preventing HCMV latent infection in THP-1 cells (Keyes et al., 2012). Kawasaki et al. (2007) reported that CsA and Cyps-specific inhibitor NIM811 decrease MCMV replication by preventing immediate-early (IE) gene expression in neural stem and progenitor cells (NSPCs).

In case of HIV, by defusing the enzymatic activity of CypA, CsA can disrupt the HIV-1 CA-CypA interaction (Li at al., 2009; Schaller et al., 2011) and compete with virion CA for binding to target cell CypA. CsA also decreases gp120 and gp41 incorporation into HIV-1 virions, which weakens the fusion of these virions to susceptible target cells (Sokolskaja et al., 2010). CsA and Cs can also disrupt CA-CypA interaction in HeLa cells, (Hatziioannou et al., 2005; Ylinen at al., 2009). All these reports demonstrate that targeting cellular CypA is quite helpful to overcome HIV-1 CA-mediated infections (Sokolskaja et al., 2010). Cyclosporine A and other nonimmunosuppressive CypA inhibitors (CsA analogues) such as Debio 025, NIM811, and SCY-635 disrupt the HCV-CypA complex and block HCV replication by defusing the enzymatic functions of CypA both *in vitro* (Mathy et al., 2008; Chatterji et al., 2009; Kaul et al., 2009; Lee, 2013) and *in vivo* (Flisiak et al., 2009; Hopkins et al., 2009), as CsA can abrogate the CypA stimulated domain II RNA binding activity (Foster et al., 2011). CsA and SCY-635 interrupt the CypA-NS5A (Chatterji et al., 2010; Hopkins et al., 2012) and CypA-NS5B complexes and abrogate HCV-RNA replication (Liu J, et al. 1991; Chatterji et al., 2009; Goldstone et al., 2010). CsA and alisporivir (ALV) could inhibit HIV-1 and HCV combined infection by preventing their respective interactions with CypA (Chatterji et al., 2010). CPI-431-32, as an analog of CsA, inhibits the isomerase activity of CypA more efficiently than CsA and ALV, and is effective in prevention of HCV and HIV co-infections (Gallay et al., 2015). Disrupting this critical interaction of a cellular chaperon protein CypA with HCV by CypA inhibitors results in prevention of HCV infection (Kaul et al., 2009), and is recommended for further studies to control HCV infection. A recent study demonstrated that lead 25, a bis-amide derivative 5, can bind with CypA and has a potent anti-HCV activity. Unlike cyclosporin A, the lead compound 25 successfully inhibits the viral replication, can restore host immune responses without acute toxicity in *vitro* and *in vivo*, and exhibits a high synergistic effect in combination with other drugs (Yang et al., 2015).

CsD Alisporivir, NIM811 and Cs and FK506 derivatives strongly inhibit the replication process of human CoV (HCoV-NL63) in cell culture. The results of qPCR discovered that all these drugs can diminish viral replication by four orders of magnitude to background levels, revealing that targeting CypA exhibits antiviral results (Carbajo-Lozoyaa et al., 2014). Cs inhibits flavivirus replication during RNA synthesis in cell culture at nontoxic concentrations by preventing CypA from making complex with NS5 protein of WNV as showed by biochemical analysis (Qing et al., 2009). CsA by binding with CypA can impair EV71 proliferation in rhabdomyosarcoma (RD) cells with non-cytotoxic concentration (Qing et al., 2014). Molecular CypA inhibitors assisted by 1-(benzoyl)-3-(9H-fluoren- 9-yl)-urea inhibit CypA and can decrease EV71 replication (Ni et al., 2009). The chemical molecule NITD008 confers a potent anti-EV71 activity by inhibiting the CypA enzyme activity (Yan et al., 2015). CypA inhibition through CsA and its analog SDZ-211-811 inhibits VSV replication more radically for New

Jersey (VSV-NJ) type than Indiana (VSV-IND) type, since CsA application reduces the initial replication of VSV-NJ by 85-90 %, while only by 10% with VSV-IND (Boss et al., 2003). Interestingly, VSV-NJ inhibition is not clacineurin dependent, since neither calcineurin inhibitors (Taigen et al., 2000) nor calcineurin inhibitory drug (Alexanian and Bamburg, 1999), has effect on VSV-NJ and VSV-IND replication (Boss et al., 2003). In all these reports, inhibition of CypA PPIase activity by its inhibitors revealed disruption of its association with other CypA-binding

Table 3. CypA inhibitors used for inbibition of viral replication.

Serial No.	Inhibitor type	Cell type/Animal	Virus Species	Reference
1	Cyclosporine A	THP-1	HCMV	Keyes et al., 2012
		HumanMonocyte Derived Macrophages (MDM)	HIV-1	Schaller et al., 2011
		Huh7 cells	HCV	Chatterji et al., 2010 /Lee, 2013
		HeLa and 293T	HIV	Hatziioannou et al., 2005
		A549 cells	Influenza A virus	Hamamoto et al., 2013
		BHK, HeLa, A549 and L929	VSV	Bose et al., 2003
		BSC-40	VV	Damaso, and Moussatche 1998
		Neural stem and Progenitor cells (NSPCs).	MCMV	Kawasaki et al. (2007)
2	Cyclosporine	HepG2215, and HuH-7	HBV	Tian et al., 2010
		BSC-40	VV	Damaso and Moussatche 1998
		HeLa	HIV-1	Ylinen at al., 2009
		CaCo-2	humanCoV (HCoV-NL63)	Carbajo-Lozoyaa et al., 2014
		Huh-7.5	Flavivirus	Qing et al., 2009
		Rhabdomyosarcoma (RD)	EV71	Qing et al., 2014
3	Cyclosporine D	CaCo-2	Human CoV (HCoV-NL63)	Carbajo-Lozoyaa et al., 2014
4	Cyclosporine G	BSC-40	VV	Damaso and Moussatche 1998
5	Alisporivir	HepG2215, HepaRG and HuH-7	HBV	Phillips et al., 2015
		Huh7 cells,	HCV	Chatterji et al., 2010; Lee, 2013
		CaCo-2 cells	Human CoV (HCoV-NL63)	Carbajo-Lozoyaa et al., 2014
6	NIM811	HepG2215, HepaRG and HuH-7	HBV	Phillips et al., 2015
		Neural stem and progenitor cells (NSPCs).	MCMV	Kawasaki et al. (2007)
		Huh7	HCV	Chatterji et al., 2010; Lee, 2013
		Human	HCV	Flisiak et al., 2009
		CaCo-2	Human CoV (HCoV-NL63)	Carbajo-Lozoyaa et al., 2014
7	Telbivudine	HepG2215, HepaRG and HuH-7	HBV	Phillips et al., 2015
8	SCY-635	Huh7	HCV	Chatterji et al., 2010; Lee, 2013
		Human	HCV	Flisiak et al., 2009
9	Deb025	Human	HCV	Flisiak et al., 2009
10	lead 25 (a bis-amide derivative 5)	Huh7.5 cells	HCV	Yang et al., 2015
11	CPI-431-32	CD4+ T-lymphocytes and Huh7.5.1	HCV and HIV co-infections	Gallay et al., 2015
12	CsA/FK506 derivatives	CaCo-2	Human CoV (HCoV-NL63)	Carbajo-Lozoyaa et al., 2014
13	NITD008	Mouse B and T cells	EV71	Yan et al., 2015
14	Anti-CD147 antibody	HepG2215, and HuH-7	HBV	Tian et al., 2010

proteins (like HIV Gag polyprotein) and resulted in subsequent ceased replication (Luban et al., 1993). Because CypA remains unavailable to interact with other proteins involved in CypA rearrangement when engaged with inhibitors, this bonded complex (CsA-CypA) could promote the binding of a third partner to the complex, preventing CypA movement to virosomes (Castro et al., 2003) (Table 3).

CsA can inhibit influenza A virus replication via CypA-dependent maner (Liu X et al., 2012) by impairing late stages like protein assembly or budding in A549 cells, while fails to inhibit its propagation in CypA deficient A549 cells. This reveals that the type of inhibition is CypA-dependent (Hamamoto et al., 2013) Table 3.

Conclusions and future view point

The present information lead us to the conclusions that cytosolic CypA interferes with the replication process of viruses, which either facilitates (such as HIV) or inhibits (Influenza) viral replication at different stages of their life cycle. However in either case, either silencing CypA via siRNA or inhibit by inhibitors, directly correlates with the attenuation or inhibition of infection respectively. Therefore, it is suggested that they could be targeted for the development of novel-antiviral therapies in order to overcome viral diseases.

Despite the body of knowledge discussed here regarding the involvement of CypA in viruses replication, the molecular mechanisms underpinning the precise role of this cellular factor remains unknown, suggesting that more interest may focus on CypA inhibitors for searching new therapies to overcome viral diseases. For example, it is unknown whether CypA merely bound with HBsAg or incorporate into the HBV viral particles or can do both coupled with the question that how SHBs regulate CypA secretion (Tian et al., 2010). The role of CypA in the proper folding of VV proteins during the formation of the internal core structure, the uncoating of viral cores (Castro et al., 2003) and the exact role in lytic and latent HCMV infection by cellular CypA, needs to be discovered (Keyes et al., 2012).

The accurate molecular pathways of CypA-HCV/HIV complex formation and the critical mechanism by which CypA promotes their replications need further exploration. To determine whether NS5A, NS5B, both, or another viral protein represent(s) the true ligand(s) for CypA will provide exact target for the development of alternative anti-HCV therapies (Chatterji et al., 2009). The precise molecular pathway of CypA-dependent regulation of EV71 replication, assembly and secretion are awaited for exploration (Qing et al., 2014). The requirement of VSV-NJ for CypA for its replication and the possible association of CypA in other subtypes of VSV-IND and/or VSV-NJ needs detailed studies (Bose et al., 2003). Furthermore, the accurate molecular mechanism of anti-influenza virus activity of CypA and CsA (CypA dependent) needs further clarification (Hamamoto et al., 2013). The mechanism of CypA association in JNK signals to facilitate IFN-b production and the critical role in the inhibition of RV protein expression required clearification (He et al., 2012, 2013). Targeting CypA via inhibiting agents with no cytotoxicity in *vitro* and *in vivo*, potent anti-viral activity and having high binding affinity for CypA are required for viral infection therapies. The advantage of targeting host factors for viral therapies is the higher genetic barrier to the emergence of viral escape mutants (Yang et al., 2015). Inlast, the findings discussed here would provide a base in understading CypA role in viral infection and development of novel anti-viral agents.

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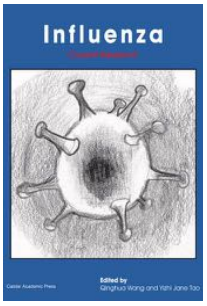

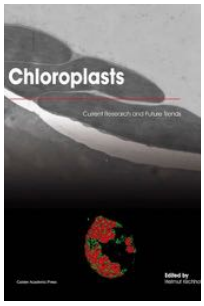

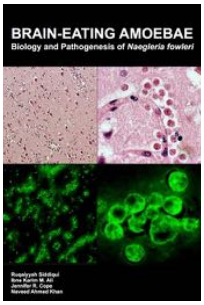

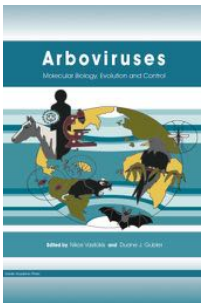

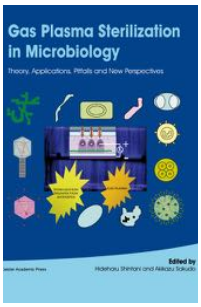

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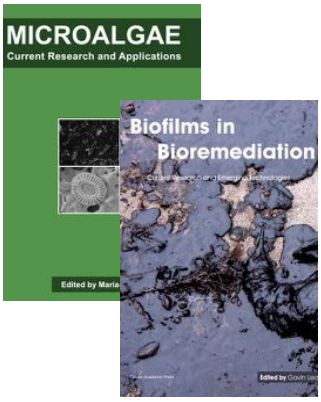

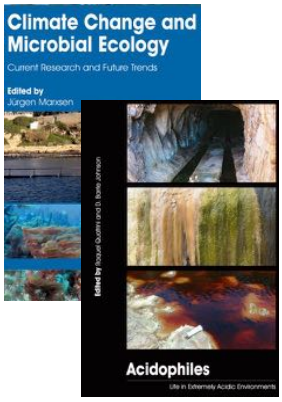

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