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Mini Review

Cyclophilin A and viral infections

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ABSTRACT

Cyclophilin A (CyPA) is a peptidyl-prolyl cis/trans isomerase originally identified as the target of the immunosuppressive drug cyclosporine A. A number of reports have demonstrated that CyPA plays a critical role in the successful replication of viruses such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), etc. However, recent studies demonstrated that CyPA also possesses a repressive effect on the replication of some viruses like Influenza A virus and rotavirus. Moreover, CyPA could also regulate host IFN-I response to viral infections. Together, these evidences showed diverse roles of CyPA in viral infection.

1. Introduction

CyPA belongs to a family of highly conserved and ubiquitous proteins known as cyclophilins (CyP). This family possesses peptidyl-prolyl cis/trans isomerase activity [1] and acts as an acceleration factor in protein folding and assembly. Till now more than 10 members of CyP subtypes have been found in mammals, including CyPA, CyPB, CyPC, CyPD, CyPE, CyP40, RanBP2, etc. Among them, CyPA is the most abundant subtype and is widely distributed in almost all tissues. In addition to its role in protein folding and assembly, the PPIase activity of CyPA has recently been demonstrated to have other roles, including intracellular trafficking, signal transduction, transcription regulation, cell cycle regulation, and stress response [2].

CyPA is commonly believed to be an important immune molecule. CyPA was originally identified as the target of the immunosuppressive drug cyclosporine A (CsA), which is used clinically for the prevention of graft rejection after organ transplantation [3]. In mammals, CsA–CyPA complex binds to and inhibits calcineurin (CN), prevents the dephosphorylation and nuclear translocation of NF-AT, and at last leads to immunosuppression [4]. CyPA plays a vital role in regulating immune response. CyPA-knockout mice have an "allergic" phenotype with increased serum IgG1 and IgE levels and tissue infiltration by mononuclear cells, eosinophils and mast cells. This phenotype is related to increased and dysregulated activity of Th_2 $CD4^+$ T cells [5]. Interleukin-2 tyrosine kinase (Itk) is a member of the Tec family of SH_2/SH_3-containing tyrosine kinases and participates in the signal transduction cascade leading to T cell activation [6,7]. CyPA binds Itk and negatively regulates its activity. In CyPA-knockout cells, Itk is constitutively activated. Thus, CyPA plays a suppressive role in the development of $CD4^+$ T cell responses through its interaction with Itk.

In recent years many studies showed that CyPA was involved in the pathogenesis of viral infection [8], cardiovascular disease [9] and cancer [10]. For example, CyPA expression can be upregulated in viral infections and correlates with final result of infection [11,12]. CyPA plays a critical role in the successful replication of viruses such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), etc. However, CyPA possesses a repressive effect on the replication of some viruses like Influenza A virus and rotavirus. In this review we focused our interest on these diverse roles of CyPA in viral infections. Moreover, the emerging function of CyPA on regulating host IFN-I response to viral infections was also discussed.

2. CypA and HIV-1 infection

CyPA gene polymorphisms have been demonstrated to influence susceptibility to HIV-1 and disease progression. A1604G and C1650G in the promoter region of the CypA gene might affect CypA expression levels and thus affect host susceptibility to HIV-1 and disease progression [13]. Furthermore, the A1650G polymorphism in the regulatory region of CypA gene may also be associated with protection from HIV-1 infection in participants of the Amsterdam Cohort Studies on HIV-1 infection and AIDS [14]. HIV-1 replication was decreased in human $CD4^+$ T cells when CyPA was knocked out [15]. These studies suggest CyPA may play an important role in promoting HIV infection.

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2.1. Interaction between CyPA and HIV capsid proteins (CA domain)

The efficient incorporation of CyPA into the HIV-1 virion is mediated through the direct binding of the prolyl peptide bond, located in a proline-rich loop of the fourth and fifth helices of the HIV-1 CA, and the active sites of CyPA in the context of Gag polyprotein [16]. Importantly, the proline residue at position 90 (P_{90}) and the glycine residue at position 89 (G_{89}), which are both highly conserved among HIV-1 Gag polyproteins, appear to be important for this interaction [17]. CyPA is packaged into HIV-1 virions during viral replication at a molar ratio of 1:10 CyPA/CA [18]. Disruption of its incorporation by Gag mutations or by treatment with CsA attenuated the infectivity of progeny viruses [19]. Therefore, packaging of host CyPA into HIV particles is an important step in HIV morphogenesis and essential for HIV replication.

2.2. Interaction between CyPA and HIV accessory proteins

The viral protein R (Vpr) of HIV-1 is the major virion-associated accessory protein that affects a number of biological functions in the retroviral life cycle, including promotion of the transport of the pre-integration complex into the nucleus and the induction of G2 host cell cycle arrest [20]. The investigation of conformational heterogeneity of the proline residues in the N-terminus of Vpr suggested a functional interaction between Vpr and a host CyPA [21]. CsA blocked expression of Vpr without affecting Vpr transcription, intracellular transport, or virus incorporation. Similarly, Vpr expression is also reduced in HIV-1 infected CyPA-knockout T cells [22]. In the absence of CyPA activity, the Vpr-mediated cell cycle arrest is completely lost in HIV-1-infected T cells. However, other study showed an opposite opinion that the interaction with CyPA is not essential for the induction of G2 cell cycle arrest by Vpr [23].

Nef is another HIV accessory protein. It is believed that optimal HIV-1 infectivity requires the presence of both Nef and CyPA during virion assembly and these factors facilitate a step in the viral life cycle between penetration and reverse transcription. A genetic dissection study of the relative contributions of Nef and the cyclophilin A-Gag interaction to HIV-1 infectivity demonstrated that Nef was not required for incorporation of CyPA into HIV-1 virions and vice versa. Surprisingly, CyPA-deficient virions remained sensitive to inhibition by CsA, in a manner that was strongly dependent on the presence of a functional Nef gene [24]. CypA–Nef fusion protein enhanced the infectivity of Nef-defective HIV-1 particles and was specifically incorporated into the virions via association with Gag during particle assembly [25]. Together, these results demonstrate that Nef and CyPA may act independently but complementary to render HIV-1 particles fully infectious.

2.3. Interaction between CyPA and CD147 in HIV infection

CD147 has been identified as the main signaling receptor for CyPA on human leukocytes [26]. CD147–CyPA interaction may regulate an early step in HIV-1 replication [27]. CyPA–CD147 interaction might induce MA phosphorylation to regulate the detachment of the RT complex from the membrane or promote transition from the step of hemifusion to complete fusion, allowing liberation of the RT complex into the cytoplasm [28]. On the other hand it is proposed that CyPA–CD147 interaction might indirectly affect CA conformation leading to destabilization of the CA shell [29]. CyPA mediates HIV-1 attachment to target cells via heparans, and heparans facilitate CyPA–CD147 interaction by first binding CyPA and then presenting it to CD147 [30]. Therefore, CyPA–CD147 interaction may be downstream of CyPA–heparan interaction. Moreover, the facilitative effect of CyPA–CD147 interaction on HIV-1 replication is signaling-independent but probably through specific events mediated by the cytoplasmic domain of CD147 [31].

3. CyPA in HCV infection

3.1. Interaction between CyPA and HCV NS proteins

Similar to HIV-1, there were several evidences that CyPA is also required for HCV replication. Knockdown of endogenous CyPA significantly hampers HCV RNA replication and viral protein expression [32] and mutation of the residues that reside in the hydrophobic pocket of CyPA (histidine in position 126 and arginine in position 55) failed to restore HCV replication [33]. CyPA increased the affinity of the polymerase to viral RNA by interacting with the NS5B and enhanced HCV replication [34]. These data are in accordance with the finding that the isomerase pocket of CyPA serves as a binding site for NS5B polymerase. These findings indicate that CyPA enhances HCV replication by catalyzing the comformational change of NS5B. Interestingly, recent studies suggest that CyPA inhibition may also act on the HCV NS5A protein. NS5A is anchored to the cytoplasmic side of endoplasmic reticulum (ER) membrane via an amphipathic N-terminal α-helix [35] and is composed of three cytoplasmic domains: D1 (residues 27–213), D2 (residues 250–342) and D3 (residues 356–447). Although sequence conservation of NS5A-D2 and -D3 in HCV genotypes is significantly lower than D1, it was reported that NS5A-D2 from the HCV JFH1 strain was the substrate for the PPIase activities of CyPA [36]. In addition, mutations in D2 and D3 of NS5A that interacts with CyPA could significantly influence viral RNA replication and thus confer resistance to cyclophilin inhibitor [37]. Furthermore, Verdegem et al. [38] revealed that CyPA has *in vitro* PPIase activity toward some, but not all of the peptidyl-prolyl bonds in NS5A-D3. This finding provided novel insights into the structure of NS5A-D3 and suggested that the interaction with CyPA might involve more than one specific NS5A domain.

3.2. Other possible roles of CyPA in HCV replication

Besides the role as a cis/trans prolyl isomerase, CyPA has also been implicated in cholesterol transport. It has been shown that a complex consisting of CyPA, heat-shock protein 56, cyclophilin 40 and caveolin transports newly synthesized cholesterol from the endoplasmic reticulum to caveolae [39]. HCV depends on cholesterol and any disturbance in cholesterol level or distribution decreases its replication [40]. Furthermore, CyPA has been involved in transcription regulation and over-expression of CyPA was shown to interact with Sin3A/Rdp3 HDAC complexes and regulate HDAC-dependent gene silencing in yeast [41]. The orthologous complex mSin3A/histone deacetylase 2 (HDAC2) was further found to modulate the transcription of the MYC target gene, carbamoyl-phosphate synthase-aspartate carbamoyltransferase-dihydroorotase (CAD) in humans [42]. CAD is a crucial enzyme in the pyrimidine *de novo* biosynthesis that HCV replication is known to depend on [43]. So it is possible that CyPA might play some important indirect role in HCV infection.

4. CyPA in HBV infection

The HBV genome encodes the envelope proteins, the core protein, the polymerase protein and a transactivating X protein [44]. HBV produces three envelope glycoproteins collectively known as HBV surface antigen (HBsAg), including the large (LHBs), middle (MHBs), and small (SHBs) surface proteins [45]. Among them, the SHBs protein is predominant and is an important viral component that reacts with the immune system of the host. CyPA, as a target

protein interacting with SHBs proteins, was found to be markedly decreased not only in the liver of HBsAg transgenic mice, but also in an HBsAg expressing cell line. However, when supernatants from transfected cells expressing HBsAg were assayed for CyPA, the amount of CyPA was found to be higher than that from the controls, suggesting that the decrease of CyPA in HBsAg positive cells was due to increased secretion of CyPA [46]. Since both SHBs and CyPA are secreted via the vesicular secretion pathway [47], the interaction between SHBs and CyPA may be directly or indirectly bridged by some cellular components. It is likely that CyPA binds to SHBs and is secreted along with HBsAg particles. Under physiological conditions, CyPA is an intracellular protein; however, during inflammation, CyPA can be secreted [48]. Therefore, the expression of HBsAg could be speculated to affect cellular functions similar to that of inflammation, resulting in secretion of CyPA from HBsAg-positive hepatocytes. In addition, the decrease of CyPA observed in HBsAg expressing cell lines may also affect protein unfolding and contribute to the pathogenesis of HBV infections as in HIV [49].

5. CyPA in Influenza A infection

Matrix protein (M1) is the most abundant structural protein that plays a crucial role in the replication, assembly and budding of Influenza A virus [50,51]. CyPA was found in the core of the influenza virion [52] and was up-regulated upon infection by avian H9N2 influenza virus in AGS cells (a human gastric carcinoma cell line) [53]. Liu et al. [12,54] revealed that CyPA interacted with the M1 protein both *in vitro* and *in vivo* and affected the early stage of viral replication. Over-expression of CyPA restricted influenza A virus replication, while the depletion of endogenous CyPA resulted in enhanced production of influenza A virus. In addition, the infectivity of influenza virus increased in the absence of CypA. CypA had no effect on viral genome replication or transcription and it also did not impair the nuclear export of viral mRNAs. However, it was found that CypA could significantly enhance the degradation of M1 protein through the ubiquitin/proteasome-dependent pathway, indicating that CypA restricts influenza virus replication through accelerating degradation of the M1 protein. Notably, the CyPA R55A mutation could still bind to the M1 protein and inhibit influenza virus replication, suggesting that the restrictive effect of CyPA on influenza virus infection was independent of its PPIase activity.

6. CyPA in other viral infections

CyPA is also associated with the life cycle of other viruses including vaccinia virus (VV), vesicular stomatitis virus (VSV), and severe acute respiratory syndrome coronavirus (SARS-CoV) [55]. VV infection led to an impressive increase in CyPA stability whereas in VV infected cells, CyPA relocalized to the peripheral region of the nucleus, colocalizing with sites of virus production. CyPA was then incorporated into the virus particle during morphogenesis and localized specifically in the core [1]. In addition, CyPA has been found associated with VSV, a negative stranded RNA virus. CyPA interacts with the nucleocapsid protein of VSV and, like VV, incorporated into VSV viral particles where it likely acts as a chaperone for the nucleocapsid protein that wraps the genomic RNA to produce the functional template for transcription [56]. CyPA was also reported to regulate SARS-CoV replication through binding to the nucleocapsid protein and being incorporated into particles [57,58]. Rotavirus (RV) infection is the main cause of acute dehydrating diarrhea in infants and young children below 5 years old worldwide. Our study showed that RV infection triggered a temporal increase of CyPA protein. In RV infection, CyPA was recruited to the viroplasm of RV in MA104 cells and herein interacted with RV structural protein VP2 to repress RV infectivity to MA104 cells and inhibit RV reproduction through its PPIase activity (unpublished data).

7. Roles of CYPA in host antiviral innate immunity

It has been shown that CypA is excluded from wild-type simian immunodeficiency virus (SIVagm) particles but is efficiently packaged into vif-deficient SIVagm virions. The presence of CypA in vif-defective SIVagm was correlated with reduced viral replication. Infection of CypA-knockout Jurkat cells or treatment with cyclosporine A eliminated the Vif-sensitive inhibition and resulted in replication profiles similar for wild-type and vif-deficient SIVagm [59]. Therefore, CypA was predicted as a novel vif-sensitive antiviral factor that may limit zoonotic transmission of SIVagm or HIV.

Dendritic cells have a central function in the host defence, linking innate immunity to microbes to activate pathogen-specific adaptive immunity. Recently it has been reported that CyPA in dendritic cells could recognize the newly synthesized HIV-1 CA domain and subsequently prompt a IFN-I response through activation of IRF3, which is dependent on the PPIase activity of CyPA. Thus it is concluded that CyPA functions as a cell-intrinsic sensor of viral infection able to recognize the newly synthesized viral capsid proteins [60]. In our study we also found that CyPA was required for the host IFN-I response in RV infection of MA104 cells, however, this was not dependent on PPIase activity but on the JNK signaling pathway [61].

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