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Potential roles of protein disulphide isomerase in viral infections

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Summary. – Protein disulphide isomerase (PDI) family members are predominantly endoplasmic reticulum (ER)-bound chaperonic proteins, which have also been shown to be present on the cell surface. Some of them have been found to be associated with lipid rafts, MHC class I, and cell-signaling molecules such as signal transducer and activator of transcription (STAT) proteins in certain viral infections. Since there is evidence suggesting that PDIs have a role in the virus entry to the cell, they obviously play an important role in virus-host interactions and viral pathogenesis. In this review, we discuss potential roles of PDIs in viral infections, in order to disclose new antiviral therapeutic targets.

Keywords: protein disulphide isomerase; virus; chaperone

Contents:

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Abbreviations: DNV = dengue virus; PDI = protein disulphide isomerase; STAT = signal transducer and activator of transcription; EBV = Epstein-Barr virus; ER = endoplasmic reticulum; ERAD = ER-associated degradation; Ero 1 = endoplasmic reticulum oxidoreductin 1; HIV = human immunodeficiency virus; HPV = human papillomavirus; IL = interleukin; IFN = interferon; PyV = polyomavirus; NS = non-structural

1. Introduction

The emerging and re-emerging viral diseases have become a global threat. It is an important public health concern and poses many challenges to the scientific community to discover and develop new treatment strategies. Immediate measures and antiviral drugs are required for treating sudden viral disease outbreaks. There is an urgent need to control viral infections, making it necessary to understand the mechanisms that viruses use to evade the host immune system and the manner in which they overtake and utilize the host machinery to replicate and persist. In this pursuit, novel antiviral agents such as plant derived compounds and chemical inhibitors may be developed and used to control viral persistence. Understanding the interaction of virus with its host and the mechanism of initial viral entry and replication is required to devise strategies to nip the infection in the bud. A distinctive feature of some viruses is their ability to manipulate host protein networks to work in their favor. Strategies employed by viruses include secretion of cytokine homologues and the synthesis or induction of proteins such as PDI.

PDI is a part of 20 member PDI family in humans and is expressed ubiquitously (Kozlov *et al*., 2010). It is primarily an ER resident protein; however, it has also been found to be localized in the plasma membrane, mitochondria, phagosomes, nuclear envelope, and other parts of the cell

(Akagi *et al.*, 1988; Rigobello *et al.*, 2001; Turano *et al.*, 2002; Desjardins, 2003). It is a well characterized enzyme belonging to the thioredoxin superfamily (Klappa *et al.*, 1998). PDI proteins are almost omnipresent in the cell. Members of the PDI family of proteins have the potential to oxidize nascent proteins as well as identify misfolded proteins and direct their degradation via the unfolded protein response, ER-associated degradation (ERAD) and thus play a vital role in maintenance of ER homeostasis (Lee *et al.*, 2010; Sato *et al.*, 2011). PDI and ERp57 which are ER resident proteins are typically involved in the formation and rearrangement of disulphide bonds and in the proper folding of newly synthesized protein in the rough ER. Subsequently, these proteins are either trafficked to the cell membrane or secreted. It is interesting to note that cell-surface PDI is involved in the regulation of leukocyte adhesion (Bennett *et al.*, 2000) and also in platelet adhesion (Essex *et al.*, 2001) by mediating reduction or rearrangement of disulphide bonds. The PDI enzyme is composed of two thioredoxin (Trx)-like, catalytic domains, a and a′, separated by two non-catalytic domains, b and b′ (Alanen *et al.*, 2003). The arrangement of the domains varies among the members of the PDI family (Kozlov *et al.*, 2010). PDI has a typical polypeptide binding ability that is non-specific, accounting for its chaperonic function (Wang and Tsou, 1993).

The ER has an oxidizing environment as compared to the reducing environment of the cytosol; this facilitates disulphide bond formation in the ER by the PDI family members and other proteins. Mammalian ER localized PDI is oxidized by ER oxidoreductin 1 (Ero1) α or β, which in turn oxidizes and forms disulphide bonds in its substrates (Cabibbo, 2000). PDI members like ERp57 and ERp72 are also oxidized by Ero1 but to a lesser extent apparently due to the low hydrophobicity of their b′ domain (Kozlov, 2006, 2009), which is the peptide or non-native protein binding site. The CXHC active site motif present in one or more domains is common to the PDI members PDI, PDIp, ERp57, ERp72, P5, ERp46, TMX3, ERdj5, and PDIr, which are primarily thiol-disulphide oxidants (Ellgaard and Ruddock, 2005). However, ERdj5 contains CXPC motif in 3 of its active sites which is commonly found in thiol-disulphide reductants (Ellgaard and Ruddock, 2005). ERp44 is involved in ER retention of proteins like Ero1 by forming stable mixed disulphides (Anelli *et al.*, 2002, 2003). ERp57 catalyzes isomerization much more efficiently than oxidation via its interaction with calreticulin and calnexin (Mezghrani *et al.*, 2001; Jessop *et al.*, 2007).

In the past decade, research has been driven towards understanding the functioning of PDI in the context of viral infections and it has been found to be involved in aiding viral entry, infection and multiplication (Table 1). Cell surface PDI has been shown to be involved in human immunodeficiency virus (HIV) (HIV-1 and/or HIV-2) envelope mediated membrane fusion after CD4 binding (Fenouillet *et al.*, 2001, 2007; Gallina *et al.*, 2002; Markovic *et al.*, 2004; Papandréou *et al.*, 2010). Mishra *et al.* (2012) have shown that silencing of PDIA3 (ER-resident protein or ERp57) leads to decreased intracellular viral load, thereby confirming that PDI helps dengue virus (DENV) to multiply within the host cell. Involvement of other PDI family proteins have been shown in polyomaviruses, rotavirus, Newcastle disease virus and human papillomavirus (HPV) infections as well. Moreover, ERp57 is a vital protein in MHC class I associated antigen presentation wherein it interacts with the peptide loading complex. The peptide loading complex includes calreticulin, tapasin, ERp57, and the TAP transporter (Park *et al.*, 2006; Kim *et al.*, 2009; Lee *et al.*, 2009). This review provides an integrated understanding about the role of PDI family of proteins in the context of viral infections not only on the cell

Table 1. Participation of PDI family members in human viral infections

PDI member	Virus	References
PDI (PDIA1)	Human immunodeficiency virus	Fenouillet *et al.*, 2001; Gallina *et al.*, 2002
	Epstein-Barr virus	Loesing *et al.*, 2009
	Dengue virus	Chua *et al.*, 2004; Valle *et al.*, 2005; Cheng *et al.*, 2009; Chen *et al.*, 2009; Wan *et al.*, 2012
	Polyomavirus	Rainey-Barger *et al.*, 2007; Tsai and Qian, 2012; Walczak and Tsai, 2011; Walczak *et al.*, 2012
	Simian virus 40	Schelhaas *et al.*, 2007; Goodwin *et al.*, 2011; Walczak *et al.*, 2012
	Hepatitis C virus	Wang *et al.*, 2006
ERp57 (PDIA3)	Dengue virus	Mishra *et al.*, 2012
	Polyomavirus	Walczak and Tsai, 2011
ERp72 (PDIA4)	Polyomavirus	Walczak and Tsai, 2011
	Papillomavirus	Campos *et al.*, 2012
ERp29	Polyomavirus	Walczak and Tsai, 2011
PDIp (PDIA2), PDIR (PDIA5), P5 (PDIA6), PDILT, ERp44, ERdJ5, ERp46, ERp27, ERp18, ERp90b	Interaction not found	

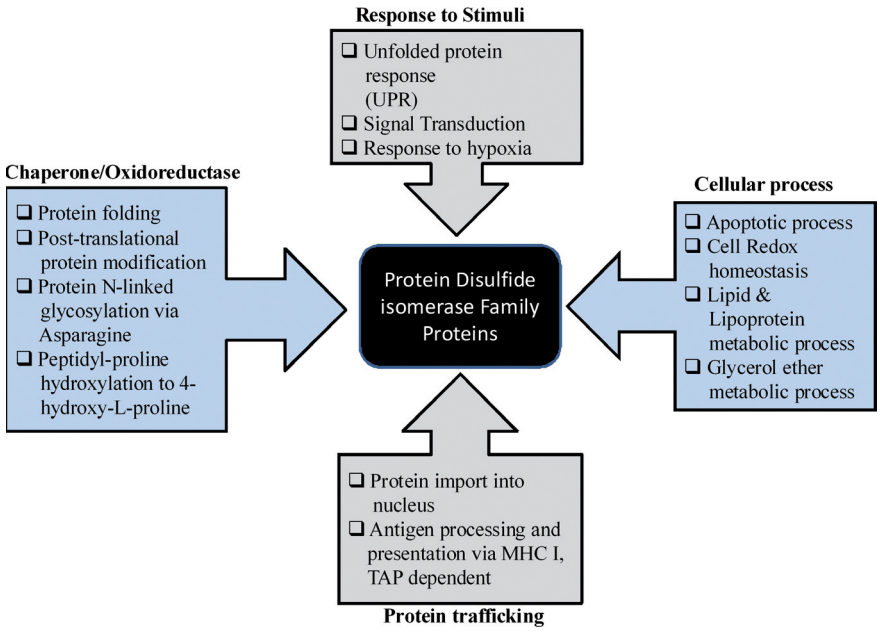

Fig. 1

Functional diversity of PDI family members

surface (eg. HIV entry), but also in intracellular processes (eg. Epstein-Barr virus (EBV) infection).

2. PDI

2.1 Functional role of PDI

PDI is expressed in all multicellular organisms and its biochemical and structural properties have been elucidated (Wang and Tsou, 1993; Freedman *et al.*, 1998; Wilkinson and Gilbert, 2004), however, what remains to be answered is, why the cell needs several proteins with apparently the same catalytic and chaperonic functions, their wide range of substrate targets in different tissues and interactions that steer several disease states. The PDI family members are involved in a variety of cellular processes, as depicted in Fig.1.

The formation of disulphide bond in nascent protein is a way to stabilize and protect it from over oxidation by reactive oxygen species and other molecules during stressful conditions such as those brought about by infections. Formation of such a bond is a rate limiting step, which is catalyzed by enzymes like PDI *in vivo*.

2.2 Catalytic functions of PDI

The X-X residues in the CXXC motif of the catalytic domains a and a′ of PDI, determine the redox potential of the enzyme, and drives its catalytic function as a thiol-disulphide reductase (Fig. 2), oxidase, or isomerase (Ellgaard and Ruddock, 2005). In the oxidized state, the domain conformation of PDI can accommodate substrate proteins with high affinity and chaperone the formation of native

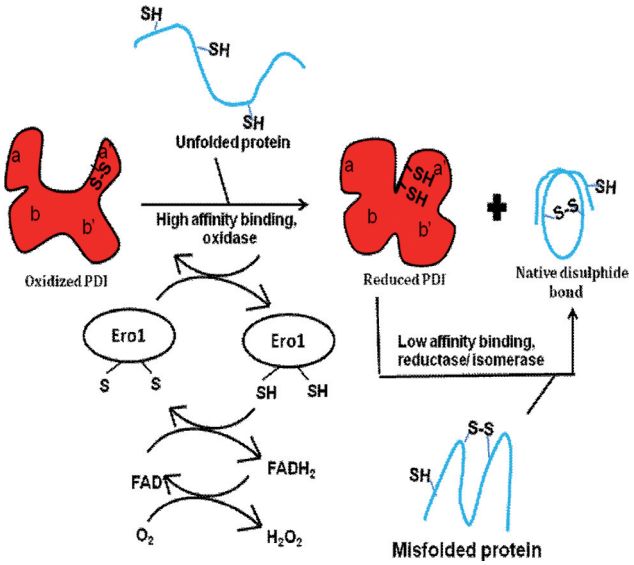

Fig. 2

Catalytic and chaperone functions of PDI

bonds. When PDI is reduced, conformation of PDI domains is more compact, allowing low affinity binding to misfolded protein substrates, subsequently catalyzing reduction or isomerization of disulphide bonds.

The catalytic function of PDI moreover, depends on the redox potential of the ER, which is influenced by the ratio of reduced to oxidized glutathione in the ER (GSH:GSSG::2:1) (Hwang *et al*., 1992) as well as influx of oxidizing agents in the ER in the following modes (Depuydt *et al*., 2011):

1) when PDI cysteine is oxidized: electron transfer from substrate proteins to the CXXC motif of PDI may occur via interaction of PDI with other folding proteins; aiding proper disulphide bond formation.
2) when PDI cysteine is reduced: PDI can react with non-native disulphides and form mixed disulphide complex, which either after attack of the second cysteine can result in release of oxidized PDI or alternatively thiolate of the substrate may attack the mixed disulphide resulting in reshuffling of the disulphide within the substrate protein and release of PDI with no change in its redox state.
3) regulation of PDI by ER oxidoreductin 1 (Ero1): Ero1 is an ER resident flavoprotein which has 4 cysteine residues and 2 more pairs of regulatory cysteines in addition. The cysteine residues of Ero1 are reduced by PDI, Ero1 transfers electrons to flavin adenine dinucleotide (FAD) which transfers it to molecular oxygen, generating H_2O_2. The regulatory pair of cysteine residues of Ero1 regulates the H_2O_2 levels and maintains optimal redox potential of the ER for disulphide bond formation. They are oxidized when the redox conditions in the ER become too oxidizing, restricting the movement of the flexible loop of Ero1 so PDI can not transfer electrons to the catalytic center of Ero1, and is therefore, available to form mixed disulphide complex as described above. However, under highly reducing conditions in the ER the regulatory cysteines are reduced, allowing the transfer of electrons from PDI to the CXXC motif of the flexible loop and further to flavin adenine dinucleotide (Sevier *et al*., 2007).

2.3 Chaperone function of PDI

Protein folding tends to render distinct conformational states to unfolded proteins. *In vivo* folding of proteins is concurrent with protein synthesis, referred to as co-translational folding, which is not a very accurate process. Therefore, often generated aberrant or misfolded proteins may be rectified by quality control chaperones and foldases of the ER or may be degraded. While some such proteins involved in quality control are localized to the ER and cytoplasm, some are extra-cytoplasmic or are found in the outer regions of the cell in eukaryotes (Powers and Balch, 2011), such as the chaperones Hsp70 and Hsp90 (Horváth *et al*., 2008). Human PDI is a redox-regulated protein and its conformational changes determine its substrate binding abilities (Wang *et al*., 2012). When human PDI is reduced, very few hydrophobic areas are exposed for substrate binding, whereas when it is oxidized, (primarily the a′ domain) it has tremendous substrate binding ability with increased exposure of hydrophobic areas (Wang *et al*., 2012). While oxidized PDI mostly binds to reduced/unfolded polypeptide chains, for the formation of disulphide bonds, the reduced PDI extends its reductase or isomerase function upon its interaction with misoxidized substrates (Hatahet and Ruddock, 2009). The ability of PDI family of proteins to bind to a large repertoire of substrates and associate with peptides or other proteins, inhibit aggregation, and render proper conformation to unfolded proteins without being altered itself, renders them to be efficient chaperones. PDI forms heteromeric enzymatic complex in the ER with prolyl hydroxylase (Pihlajaniemi *et al*., 1987) and also with microsomal triglyceride transfer protein (Wetterau *et al*., 1990). Calnexin or calreticulin, which have lectin-like activity have been found to associate with ERp57, apparently involved in the proper folding of glycoproteins (Elliott *et al*., 1997; Zapun *et al*., 1998; Oliver *et al*., 1999). Others have been known to bind calcium (Macer and Koch, 1988), ATP (Nigam *et al*., 1994; Quemeneur *et al*., 1994), and smaller ligands like estradiol (Tsibris *et al*., 1989). These proteins therefore have chaperonic functions by virtue of their ability to interact with several other proteins mediating cellular responses and are also over expressed during stress (Jansen *et al*., 2012).

3. Role of PDI in virus infections

3.1 Herpesviruses

The herpesviruses have around 25 members, 8 or more of which infect humans and belong to the *Herpesviridae* family. They typically have a linear, double stranded (ds), DNA genome, encapsulated in an icosahedral capsid core, followed by the tegument which carries viral proteins and enzymes required for viral replication and the outermost region comprises envelope protein. The viral genome is large in size coding upto 200 genes. Herpes simplex virus 1 (HSV-1), EBV, human cytomegalovirus (HCMV) and varicella-zoster virus (VZV) are some of the members of this family.

The EBV multi-spanning transmembrane envelope protein BMRF2, has been shown to interact with PDI, as they co-localize in the ER (Loesing *et al*., 2009). BMRF2 and another EBV glycoprotein called BDLF2, have been

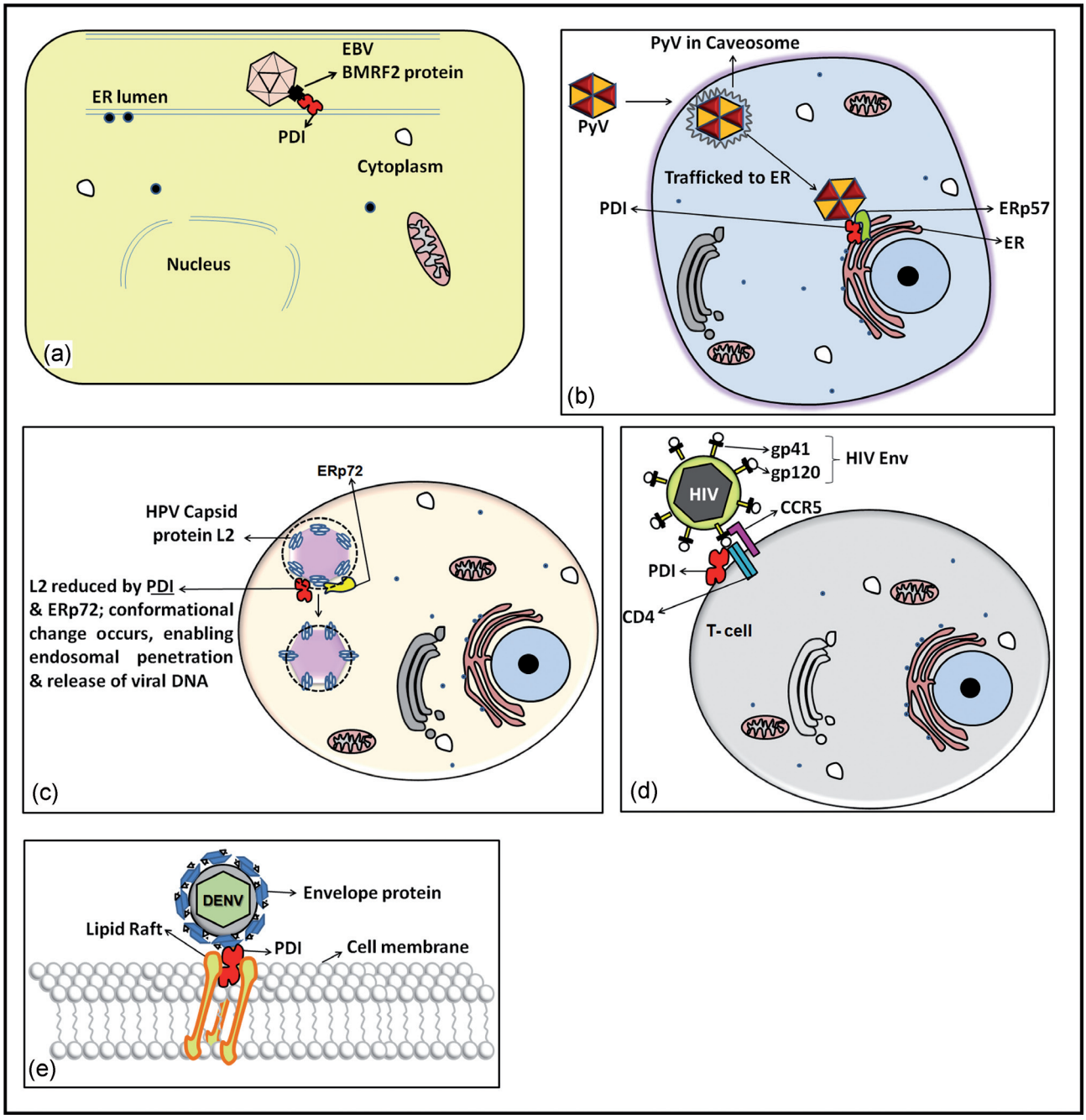

Fig. 3

Interactions of PDI with EBV, PyV, HPV, HIV, and DENV

shown to be associated with PDI in the ER, and are subsequently, transported to the Golgi network via the secretory pathway, finally reaching the plasma membrane (Fig. 3a). The protein complex alters the actin cytoskeleton of the cell (Loesing *et al.*, 2009) and the RGD motif of protein complex on the major extracellular domain of BMRF2 engages cellular integrin receptors (Tugizov *et al.*, 2003), altering the cell shape, forming extended cellular processes and thus increasing spread of the infectious virus to the adjoining cells.

3.2 Polyomaviruses

Polyomaviridae family viruses are potentially oncogenic, comprising of circular, 5kb long dsDNA, enclosed in an icosahedral capsid with no envelope coating. The genome has six genes namely; large T-antigen, small t-antigen, viral protein (VP) 1, VP2, VP3, and agnoprotein. Polyomaviruses utilize ER oxidoreductases, chaperones and even the ERAD machinery to enter and infect host cells (Tsai and Qian, 2010). Human polyomaviruses include BK virus and JC virus (initials of patients in whom the virus was discovered), WU virus (discovered in Washington University), KI virus (discovered in Karolinska Institute), and Merkel cell polyomavirus. SV40 and polyomavirus (PyV) are rather widely studied and well annotated model polyomaviruses. This non-enveloped virus gains entry by interacting with the glycolipid ganglioside receptors on the host cell plasma membrane followed by endocytosis (Tsai *et al*., 2003). The virus is trafficked to the ER via the caveosome, where uncoating of the virus takes place, and subsequent translocation of the virus to the nucleus occurs (Fig. 3b) (Gilbert *et al*., 2006; Schelhaas *et al*., 2007). In ER, the PDI family members are crucial players in aiding the virus to persist by conferring conformational changes to the viral proteins and modifying disulphide bonds. ERp57 acts as an isomerase and PDI primarily chaperones the viral VP1 protein, releasing a subset of the VP1 viral particles. Subsequently, SV40 recruits Ig heavy chain binding protein (BiP) in a reaction that exposes hydrophobic moieties of the VP2 and VP3 proteins facilitating their integration into the ER membrane, controlled by the ER-resident DnaJ 3 protein (ERdj3) (Schelhaas *et al*., 2007; Goodwin *et al.,* 2011). PyV recruits another PDI family member ERp29 to expose VP2 and VP3, besides ERp57 and PDI as pre-requisites for action of ERp29 processing (Rainey-Barger *et al*., 2007). The PDI family members are involved in retro-translocation of aberrant proteins from the ER to the cytosol as part of the ERAD machinery. PyV is trafficked to the cytosol in an analogous manner and engages the ERAD protein Derlin1 members and proteasome activity (Schelhaas *et al*., 2007; Jiang *et al*., 2009; Inoue and Tsai, 2011). Downregulation of some of the PDI family proteins have been shown to inhibit PyV infection, establishing the vital role played by these proteins in viral infection via an ERAD like pathway (Gilbert *et al*., 2006; Walczak *et al*., 2011).

3.3 Papillomaviruses

Papillomaviruses comprise of non-enveloped group of dsDNA viruses, which can cause benign lesions of the skin and mucous membranes. HPV commonly cause sexually transmitted diseases. There are more than 100 HPV genotypes and they are known to cause cancer of the cervical, anogenital, head and neck regions. Campos *et al*. (2012) have performed extensive experiments to show the role of PDI in HPV infection, using a PDI inhibitor bacitracin, which inhibits HPV infection up to 95% despite the initial enhancement of viral entry. Moreover, the inhibition has been suspected to block PDI, ERp72 mediated reduction of the disulphide bond between Cys22 and Cys28 of the L2 HPV capsid protein. This reduction of L2 helps the virus to attain the proper conformation for endosomal penetration (Fig. 3c) (Campos *et al*., 2012). However, when bacitracin blocks this reaction, it prevents the transfer of viral DNA across the endosomal membrane and also results in destruction of the viral genome within the endo-/lysosomal compartment. This depicts that PDI is hand-in-glove with the virus.

3.4 Retroviruses

Retroviruses are the most baffling, biological proof for reverse transcription. They include RNA viruses that can reverse transcribe into DNA for their persistence and replication in the host cell. HIV is an RNA virus belonging to the *Retroviridae* family. It belongs to the genus *Lentivirus,* carries positive sense single stranded (ss), enveloped, 7–10 kb long RNA genome, with a 5′-cap and 3′-poly(A) tail and causes AIDS (Weiss, 1993). The viral genome includes two copies of the 9.5 kb long ssRNAs, encoding Gag, Pol, Env, Tat, Rev, Nef, Vif, Vpr, and Vpu. Gag is cleaved to obtain matrix, capsid and nucleocapsid proteins; Pol is cleaved into protease, reverse transcriptase (RT) and integrase; and Env is cleaved into gp120 and gp41. The RNA genome, transcribed by RT, may be prevalent in the host cell in a circular episomal form or may be integrated into the host genome by the integrase enzyme. It is an enveloped virus with outer membrane composed of gp120 with transmembrane gp41 subunits. HIV primarily invades the host by infecting the $CD4^+$ T lymphocytes, via interaction of the gp120 viral protein through various chemokine and cytokine receptors (Fenouillet *et al*., 2001, 2007; Bi *et al*., 2008).

PDI has been shown to form a complex with HIV gp120, CD4 and co-receptors CCR5 or CXCR4 on T cell surface (Fig. 3d) (Fenouillet *et al*., 2001; Gallina *et al*., 2002; Markovic *et al*., 2004; Fenouillet *et al*., 2007; Papandréou *et al*., 2010). Bi *et al*. (2011) have elucidated the role of PDI in HIV infection, which involves association of PDI with galectin-9 on the cell surface of murine Th2 cells; enhancing β3 integrin mediated cell migration and HIV infection. Galectin-9 belongs to a family of mammalian lectins, expressed also by T cells. It binds to glycan ligands on specific glycoprotein or glycolipid receptors, and kills $CD4^+$ Th1 cells but not $CD4^+$ Th2 cells (Bi *et al*., 2008; Garner and Baum, 2008; Vasta, 2009; Liu *et al*., 2010). Presence of α2,6-linked sialic acids on the surface of Th2 cells,

blocks galectin-9 binding to glycan receptors; whereas, its absence in Th1 cells results in galectin-9 mediated cell death (Bi *et al*., 2008). This kind of alternative glycosylation state determining the survival of T cell subtype has been shown for the first time. Bi *et al*. (2008) have also shown that PDI, PDI family A - 3 (PDIA3), and A - 6 (PDIA6) are receptors for galectin-9. This binding of galectin-9 to cell surface PDI via O-glycan on PDI, resulted in increased retention of PDI on the murine Th2 cells; whereas, PDI expression was minimal in Th1 cells, enhancing cell migration by associating with β3 integrin. The aforesaid study also tells us that the infection of Jurkat cells with HIV is enhanced in presence of galectin-9 in a PDI dependent manner, reiterating the involvement of PDI in HIV infection. However, the apoptosis frequency, and cytokine levels in relation to HIV infection of Th2 cells, owing to the alternative glycosylation state, has not been measured by Bi *et al*. (2008). In sharp contrast to this galectin-9 mediated PDI dependent HIV infection in the surviving Th2 cells, most studies thus far have shown that HIV infection primarily involves Th1 type cells and the type 1 cytokines and that productive HIV infection of Th1 cells induces anti-apoptotic responses, by a 10 fold up-regulation of BCL-2 (Bahbouhi *et al*., 2004).

3.5 Flaviviruses

The *Flavivirus* genus is a subgroup of the *Flaviviridae* family, comprising of more than 70 members. This subgroup of viruses causes severe viral infections in humans such as dengue fever, yellow fever, and encephalitis, etc. The viruses are enveloped; containing a positive sense, 10–11 kb long, ssRNA genome packed in an icosahedral nucleocapsid. Flavivirus diseases are arthropod borne. Dengue virus species belong to the *Flavivirus* genera and include four viruses: dengue virus 1 to dengue virus 4 (DENV-1 to DENV-4). The genome encodes 3 structural (envelope, capsid and premembrane) and 7 non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Virus is transmitted to the vertebrate host by the bite of the infected *Aedes aegypti* or *Aedes albopictus* mosquito vectors. It has a 5′-cap (m7G-pppAmpN2) but lacks a 3'-poly(A) tail.

PDI, a chaperonic protein, has been implicated in viral replication, translation or encapsidation and gene expression. PDI, calreticulin and La proteins have been found to interact with the 3'-UTR (-) of DENV and other four viruses (Yocupicio-Monroy *et al*., 2003). Moreover, in the aforesaid study, PDI can interact with calreticulin *in vivo*, wherein, PDI has been shown to interact with the cis-acting elements of DENV-4 via calreticulin, which can interact with RNA sequences and La, preventing the RNA from rapid degradation. PDIA3, which is one of the PDI family members, has also been shown to help the virus and is up-regulated during DENV-2 infection, along with another host protein called heterogeneous nuclear (hn) RNP H (hnRNPH) (Mishra *et al*., 2012). PDI has been shown to be recognized by anti-DENV NS1 antibodies on platelet surface (Cheng *et al*., 2009). It is also noted that PDI shares regions of homology with DENV NS1, cross-reacts with the anti-DENV NS1 antibodies and seems to reduce platelet aggregation consequently. The role of PDI in DENV entry is evident from the fact that PDI silencing led to the inhibition of DENV entry into endothelial cells (Wan *et al*., 2012). Also, PDI was shown to co-localize with lipid rafts and DENV envelope protein on the cell surface, resulting in the activation of cell surface integrins (β1 and β3) to further facilitate viral entry (Fig. 3e) (Zhang *et al*., 2007; Wan *et al*., 2012). PDI was shown to play a role in viral replication in the host cell (Wan *et al*., 2012). As far as the mechanism by which PDI interacts with flaviviruses is concerned, studies available seem to suggest that PDI indirectly associates itself with the virus either by complexing with calreticulin, sharing homologous regions with DENV NS1, or by integrin activation.

Hepatitis C virus (HCV) is also a *Flaviviridae* family member, with approximately a 9.5 kb genome that codes for the structural (core, E1, E2 and P7) and NS (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) proteins (Choo *et al*., 1991; Reed and Rice, 2000). The HCV NS5A has been shown to interact with PDI localized in the ER (Wang *et al*., 2006).

4. Interaction of PDI with animal viruses

PDI has been found to interact with animal viruses such as the African swine fever virus (ASFV) which is responsible for causing highly contagious fatal hemorrhagic fever in pigs. This ds DNA virus belongs to the *Asfaviridae* family. ASFV codes for an enzyme called the trans-prenyl transferase (B318L), which has been shown to co-localize with PDI in the ER (Alejo *et al*., 1999). This implies that B318L seems to be closely interacting with PDI in facilitating virion assembly within the host. An interesting aspect of host cell protein PDI mimicry by viruses has been shown in pestiviruses which infect mammals. They have a positive sense, ssRNA genome and belong to the family *Flaviviridae*. The pestivirus E2 protein has been shown to contain conserved CXXC motif similar to the motifs in the catalytic sites of PDI (Krey *et al*., 2005).

5. PDI in signal transduction

ERp57/GRP58/ER-60/PDIA3 is a PDI family protein and is part of the 'Statosome' complex in the cytoplasm and on the plasma membrane rafts (Ndubuisi *et al*., 1999). It is involved in raft-STAT signaling (Sehgal, 2003). The

STAT signaling molecules STAT3, STAT1, STAT5a, and STAT5b exist as part of protein complexes in the cytosol and more proteins are added to the complex on cytokine stimulation. STAT3 containing Statosome I complex is composed of nearly eight different polypeptides, 3 out of which complex in an interleukin (IL) IL-6 dependent manner, including PDIA3 (Ndubuisi *et al.*, 1999). What is noteworthy is that when these rafts are disrupted, using methyl beta cyclodextrin which is a cholesterol inhibitor that disrupts lipid rafts, IL-6- and IFN-γ-induced STAT signaling is inhibited. IL-6 is an important cytokine being involved in inflammation and in modulating the acute phase response. Similarly, IFN-γ is a potent anti-viral molecule. ERp57 and HSP90 are part of the statosome along with STAT1 and STAT3 on the plasma membrane raft. This perhaps has the effect on several viral infections, since we now know that PDI is associated with lipid rafts on, for instance, DENV infected endothelial cell surface (Wan *et al.*, 2012). Valle *et al.* (2005) showed that lipid rafts in association with HSP70/90 complex are involved in DENV entry and infection (Valle *et al.*, 2005). Padwad *et al.* (2009, 2010) have also shown that Hsp 60 and 70 are upregulated during DENV infection in promonocytic cell line U937 and monocytic cells THP1, respectively. Hsp60 and 70 silencing lead to decreased intracellular DENV load (Valle *et al.*, 2005; Padwad *et al.*, 2009). Heat shock proteins have been shown to help the virus to multiply in the host cell in the aforesaid studies. Thus, during flavivirus infections such as dengue fever, it would be of great value to further enhance our understanding of the statosome complex proteins such as ERp57, heat shock proteins, STATs, the lipid rafts, levels of IL-6, IFN-γ, and the signaling mechanisms during viral infections. Galectin-9, a chemokine which attracts eosinophils, is induced by IFN-γ in endothelial cells (Imaizumi *et al.*, 2002), and is also associated with PDI on T-cells which facilitate HIV infection (Bi *et al.*, 2011). Here again it would be interesting to know the role of PDI in HIV infection and if IFN-γ secreted by activated T-cells promotes viral entry indirectly by stimulating galectin-9. siRNA mediated silencing of PDI was found to increase TNFα levels in DENV infected monocytes *in vitro*, indicating that PDI helps the virus and in a way under-regulates the immune response of the host against the virus (Mishra *et al.*, 2012).

5. Future directions

Research in the direction of new drugs and antiviral therapy is much needed. Mutated genotypes of viruses (HIV), the problem of antibody dependent enhancement of disease (dengue fever), and worsening of disease symptoms needs to be controlled as early as possible. The ground breaking drug Pegasys, from Hoffmann-La Roche (Switzerland), pegylated IFN-α-2a for treatment of HCV infection is now in use all over the world. This drug is a long acting IFN and manages to alleviate the infection. This draws attention to the fact that drugs need not necessarily be chemical compounds but may be modified natural defense biomolecules, which enhance and fit well into the immune system. Characterization of the mechanisms behind viral infections, host-viral interactions, and infection and immunity aspects of diseases is required to be investigated for development of novel strategies to circumvent diseases. An attempt has been made to amalgamate the existing information regarding the role of the host PDI family proteins in viral infections. PDI, ERp57 and others seem to play important roles in the viral infections discussed in this review. Presence of PDI family proteins on the host cell surface and within the cell especially in the ER seems to aid the virus in entry, assembly and persistence establishment. It would be useful to identify putative PDI-viral protein interactions and find answers to various questions. (1) At which stage of viral infection, inhibition of PDI is most effective in controlling the virus replication? (2) Is it possible to disrupt such interactions using effective anti-viral agents? (3) Are there other host proteins like PDI that help virus to enter and replicate in the host cell? (4) What are the cellular processes that are evaded by virus via PDI, etc? It would be interesting to look into possibilities to develop antiviral agents (synthetic or natural) that enhance the milieu of protective proteins such as IFN-γ, complement proteins, natural killer cell activity and at the same time downregulate host proteins like PDI that are prone to go against the host itself, proving to be a bane for the virus infected cell.

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