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Protein Disulfide Isomerase and Host-Pathogen Interaction

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Reactive oxygen species (ROS) production by immunological cells is known to cause damage to pathogens. Increasing evidence accumulated in the last decade has shown, however, that ROS (and redox signals) functionally regulate different cellular pathways in the host-pathogen interaction. These especially affect (i) pathogen entry through protein redox switches and redox modification (i.e., intra- and interdisulfide and cysteine oxidation) and (ii) phagocytic ROS production via Nox family NADPH oxidase enzyme and the control of phagolysosome function with key implications for antigen processing. The protein disulfide isomerase (PDI) family of redox chaperones is closely involved in both processes and is also implicated in protein unfolding and trafficking across the endoplasmic reticulum (ER) and towards the cytosol, a thiol-based redox locus for antigen processing. Here, we summarise examples of the cellular association of host PDI with different pathogens and explore the possible roles of pathogen PDIs in infection. A better understanding of these complex regulatory steps will provide insightful information on the redox role and coevolutional biological process, and assist the development of more specific therapeutic strategies in pathogen-mediated infections.

KEYWORDS: Host, pathogen, redox, endoplasmic reticulum, parasites, PDI, Nox

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1. INTRODUCTION

Host cells have the ability to cope with the progression and severity of infection in response to different types of pathogen. On the other hand, numerous mechanisms have evolved that support the use of the host cell machinery to facilitate pathogen survival and multiplication. Such co-evolutionary processes are directly affected by different physicochemical factors within different cell compartments, both in the host and in pathogen. For instance, pH critically affects antigen stability of the influenza virus which modulates endosome acidity that attenuates its own infection [1]. ROS (and Reactive Nitrogen Species) production and the redox state of different cell compartments are also critically involved in cellular host-parasite interaction. Among the many redox sensitive proteins that are altered during the course of different infections, protein disulfide isomerase (PDI-) mediated redox switches have been associated with pathogen attachment-internalization, antigen processing in the ER/phagosome, and the regulation of ROS production by Nox family enzymes. Thus, PDI emerges as a ubiquitous redox protein that regulates different steps of diverse infection processes. Several pathogens also have their own PDI that act as an important virulence factor (Table 1). Other redox modifications directly mediated by ROS and especially via nitric oxide (NO) generated by inducible nitric oxide synthase (iNOS), which is abundant in phagocytic cells, have been reviewed elsewhere [2, 3] and are not considered in this article. Below, the main cellular redox aspects of host and pathogen PDI will be discussed.

2. GENERAL ASPECTS OF PDI AND ITS ROLE IN HOST AND PATHOGEN

The ancient PDI is a ubiquitous redox chaperone belonging to the thioredoxin oxireductase super family and can reduce (reaction 1), oxidize (reaction 2), and catalyse dithiol-disulfide exchange reactions (i.e., isomerase activities, reaction 3, Figure 1). Such broad range of activities overlaps with the chaperone role of PDI that overall performs a housekeeping function in helping to maintain proteins in a more stable conformation. There are around 20 PDI homologues, and the detailed structure and function of eukaryotic PDIs have been covered in recent excellent reviews [4, 5]. The classic mammalian PDI (55 kDa) has several domains ordered as a-b-b′-a′-c with 2 thioredoxin-like motifs (Trp-Cys-Gly-His-Cys) displayed in the a and a′ domain [4–6] (Figure 1). PDI is abundant in the ER ($\sim$ 0.5 mM) where the relatively oxidizing conditions at basal level (i.e., GSH/GSSG ratios $\sim$ 2-3 : 1) favours PDI isomerase/oxidase activity, which is primarily involved in client protein redox folding (reaction 2-3, Figure 1). The oxidizing equivalents for this process are driven mainly by the ER thiol-containing oxidase, Ero1 (endoplasmic reticulum oxidase-1), which binds FAD and is in turn re-oxidized via electron transfer to oxygen, generating H_2O_2 in the process [7–10]. The H_2O_2 destiny is elusive, but it can oxidize ER-located peroxiredoxin IV (PrxIV) that is further reduced by PDI that is oxidized in the process [11]. This redox circuit is thought to increase total protein folding and thiol oxidation via Ero1 [11]. However, even in the absence of Ero1, protein folding still occurs, and it is suggested that other oxidases may compensate for redox demand in the ER in some circumstances [12, 13]. Nevertheless, the PDI-Ero1-dependent oxidative activity is balanced to cytosolic glutathione levels suggesting a functional redox interplay between these compartments [12]. PDI reductase activity has been primarily associated to more reducing compartments (i.e., GSH/GSSG ratios $\sim$ 30–100 : 1), such as those in the vicinity of the plasma membrane [6, 10]. PDI redox versatility is mainly governed by the low pKa of the proximal cysteine on the active N-terminal a domain. Indeed, the lower pKa of 4.5 renders PDI a much better oxidase than thioredoxin, which has a pKa of 7.1 and is mainly a reductase in most neutral pH cell compartments. It should also be noted that PDI functions as a chaperone independently of its redox-active domains as especially required for its ATPase and Ca^{2+} activity, although PDI redox motifs still stabilize binding interaction [4, 5, 10]. In the ER, PDI is tightly associated with prolyl-4 hydroxylase (the rate-limiting enzyme for collagen biosynthesis), the Sec61 translocon, and the MHC class I complex (see later). It can be also found as a heterodimer with microsomal triglyceride transfer protein [6, 10]. PDI is a soluble homodimer and does not have a transmembrane domain and, similarly to other ER chaperones, carries the KDEL C-terminal sequence which binds to respective receptors in the COP

TABLE 1: Summary of the main PDI types and redox activity expressed in different groups of pathogens.

Pathogen group	PDI (thioredoxin motif)	Redox activity	Reference
Leishmania major	5 isoforms (CGHC, CRYC)	Oxidase-isomerase	[16, 23, 24]
amazonensis	5 isoforms (CGHC, CRYC)	Reductase-isomerase	[16, 23, 24]
infantum	5 isoforms (CGHC)	ND	[23]
braziliensis	3 isoforms (CGHC)	ND	[23]
Trypanosoma cruzi	5 isoforms (CXXC)	ND	[25, 26]
Plasmodium falciparum	4 isoforms (2x CGHC)	Oxidase-reductase	[27, 28]
Toxoplasma gondii	ND	ND	[29]
Entamoeba histolytica	1 isorform, 38 kDa (2x CGHC)	Oxidase-reductase	[30]

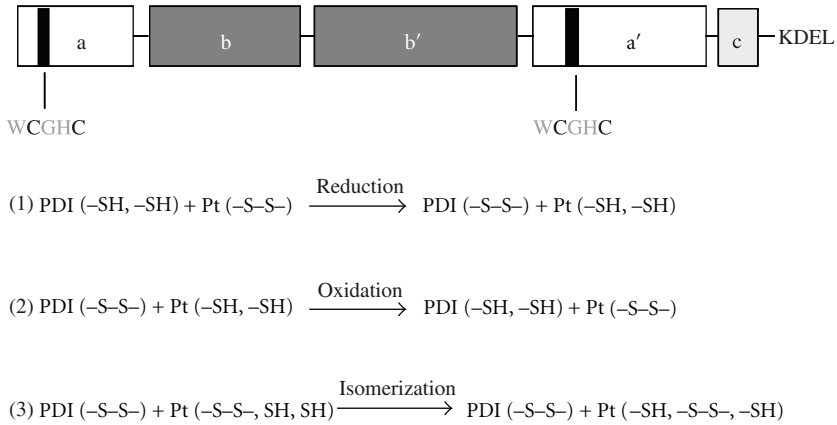

FIGURE 1: PDI and its main reactions: upper, general display of the five domains of mammalian PDI protein and showing the position of the active thioredoxin motif (WCGHC); lower, the main thiol redox reactions driven by PDI on Pt (protein/peptide) substrate containing thiols. Note that in reaction 3, the oxidation is driven by H_2O_2, especially in the oxidising ER compartment.

vesicles that circulate in the ER-Golgi vicinity, recycling proteins back to ER. PDI also undergoes intense intracellular trafficking and is found on the surface of diverse prokaryotic and eukaryotic cells [14–16]. Despite limited knowledge about this traffic, it is possible that PDI exits the ER through the translocon Sec61 pore and/or via secretory vesicles [17]. PDI is thought to attach to lipids, glycans, and integral membrane proteins via electrostatic interactions at the cell plasma membrane [14, 15], where its reductive activity mediates the infection of different pathogens (Figure 2, discussed later). PDI along with ERp57 have been found in the nuclei in association to DNA and affecting transcriptional activity of NF-kb, AP-1, and STAT3 [15]. These transcriptional regulators are key elements in many inflammatory processes, but their functional association to PDI and to different pathogen still elusive. In contrast to many other members of its family, such as thioredoxin itself and Erp57, PDI is not normally found in the cytosol, where it is likely cleaved by caspase-3 and -7 [18].

Protozoans and bacteria have their own PDIs (Table 1). The function of these PDIs in protein folding is poorly understood; however, there are intriguing data correlating PDI expression and the pathogenicity of several parasites, especially obligatory intracellular protozoans. *Leishmania* that leads to distinct types

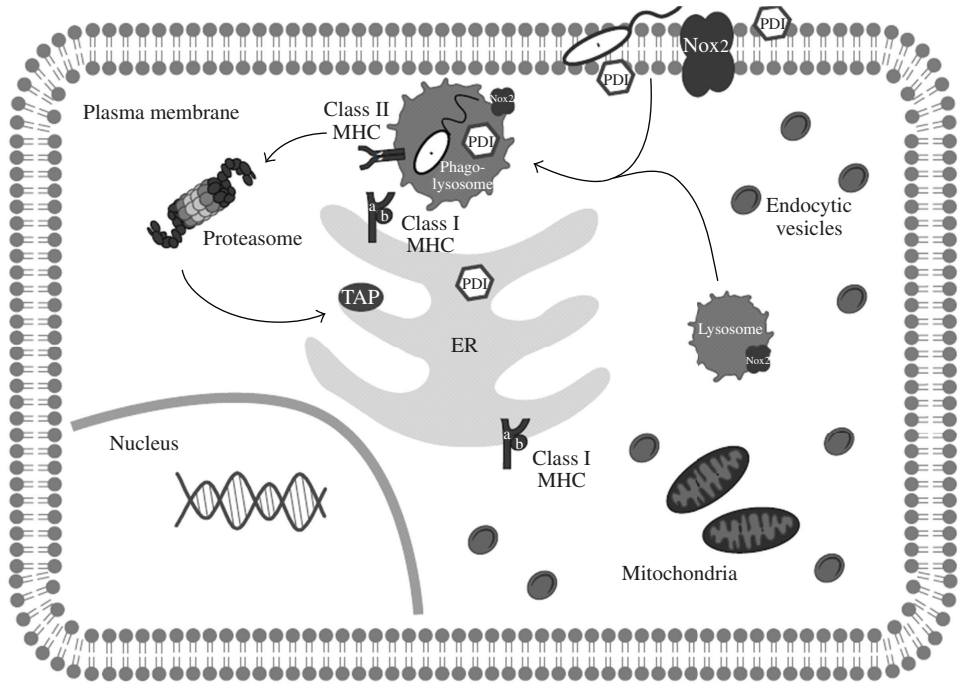

FIGURE 2: Main cellular routes involved in host mammalian PDI and pathogens.

of leishmaniases is a well-known example. The disease affects millions of individuals worldwide, and more recently this parasite emerged as an important opportunistic infection among patients with HIV [19]. There is a large variety of *Leishmania* species that results in different infection manifestation, generally classified as cutaneous (*L. major*, *L. mexicana*, *L. amazonensis*, *L. braziliensis*, etc.), diffuse cutaneous (*L. amazonensis*), mucocutaneous (*L. braziliensis*), and visceral (*L. donovani*, *L. chagasi*, and/or *L. infantum*) [20]. If *L. chagasi* is a subgroup of *L. infantum* brought to America by European colonist or other specie in its own still a matter of controversy (see discussion in [21]). The infection cycle in the vertebrate host and is initiated when *Leishmania* promastigote is injected into the skin by the insect vector. In the host, the promastigote is phagocytised especially by macrophages, and further it is converted into intracellular amastigote. Amastigote replicates inside the phagosome within the cell and is liberated after the cell lyses, subsequently infecting other cells resulting in the progression to disease [21, 22]. *L. amazonensis* has at least four PDIs, and the use of specific PDI inhibitors substantially affected parasite growth [23]. In *L. major*, the increased levels of *Leishmania* PDI (LmPDI) expression and secretion at the parasite surface reflects optimal protein folding balanced to parasite multiplication. Importantly, this is correlated to high virulence of the parasite strains [16]. More recently, the use of LmPDI antigens to generate a vaccine for *L. major* partially protected BALB/c animals and accelerated the cure of different strains of mice [24]. Similarly to *Leishmania* species, other parasites of the trypanosomatid group such as *Trypanosoma* contain several genes predicted to encode for PDIs, that can execute *N*-glycosylation and protein folding in the ER [25, 26]. Although PDI was considered essential for *T. brucei* survival, PDI activity was not essential for the growth of trypanosomes in vitro [26]. PDI is also expressed in different species of *Plasmodium* protozoans (Table 1), the parasites that cause malaria [27, 28]. *P. falciparum* expresses at least nine different PDIs and the PfPDI-8 has great similarity to the prototype PDI and is expressed during all stages of parasite life cycle. This PDI facilitates the disulfide-dependent conformational folding of EBA-175 protein, an emerging candidate for the development of malaria vaccines [28]. This is intriguing given that malaria parasites express proteins with high content of cysteine, which are associated to parasite invasion and sequestration in the vertebrate host and transmission into mosquito host [28]. Finally, *Toxoplasma gondii* PDI was identified in host tears, suggesting an extracellular location and adhesion to host cells during the initial phase of infection [29].

3. PDI AND HOST-PATHOGEN INTERACTION

Antigen presentation occur through two distinct pathways. Antigen presenting cells (APCs; especially macrophages and dendritic cells; DCs) are long-lived cells that capture antigens and subsequently process and present them at the cell surface, where they are recognized by T-lymphocytes. This process provides a long-term adaptive immune response to fungi, bacteria, and parasite. After internalization by the APC, antigens pass through phagosome/lysosome vesicles, where they form complexes with MHC class II (Figure 2), which are recognized by helper CD4+ T lymphocytes (exogenous pathway). In contrast, self cell antigens and virus synthesized within cells (mostly non-APCs) are degraded by the proteasome in the cytosol and nucleus. In successive steps, the antigen is processed, folded, and incorporated into the MHC class I (Figure 2) and the complex exposed on the cell surface, and recognized by cytotoxic CD8+ T lymphocytes (endogenous pathway). These two pathways overlap and some antigens are presented by both MHC class I and II, in a process called cross-presentation. This has been described in DCs responding to viral infection, transplant rejection, and some autoimmune diseases and cancer. Moreover, a wide range of pathogens passing or living in the phagosome such as *Mycobacterium tuberculosis*, *Salmonella typhimurium*, *Toxoplasma gondii*, and especially *Leishmania spp* and *Trypanosoma cruzi* are all cross-presented in association to high levels of $CD8^+$ T cells [31]. PDI as part of the ER protein folding machinery directly regulates antigen processing of the MHC class I complex [32–35]. Antigens that are degraded by peptidases and proteasome to shorter peptides in the cytosol and nucleus can be further transported to the ER through the TAP system, a transmembrane ER type of ATP-binding cassette (ABC) peptide transporter family [36]. ER-located PDI interacts with the peptide-loading complex (PCL) that efficiently promotes peptide assembly with MHC class I molecules and supporting the exit of the peptide-antigen complex from the ER [32–34]. Other PCL components include calreticulin, tapasin, ERp57 (another PDI family member), and the TAP transporter itself. Cells lacking PDI present much less peptide loading to MHC class I and the disulfide bridge between the peptide and MHC groove remains in a reduced redox state [32]. Normally, this interaction is affected by the redox exchange between PDI (predominantly oxidized) and ERp57 (predominantly reduced) [32], a condition in which PDI favours the release of peptide-MHC class I from the PCL and the antigen-MHCI complex is exited from ER [34]. In fact, PDI-bound peptide facilitates the disassembly of the tapasin-ERp57 complex while the PDI unbound to the complex is unable to interact with tapasin-ERp57, retaining MHC I molecules in the ER [34]. Overall, PDI redox activity modulates the stability of the antigen peptide-MHC class I complex and further determines the transport of the complex to the plasma membrane [32–35]. These redox effects may vary according to the type of antigen and some pathogens interfere with this pathway to escape antigen process and evading $CD8^+$ T-cells recognition. This is the case for US3 protein from human cytomegalovirus, which enhances PDI degradation via the proteasome [32]. PDI participation in immune response, however, goes beyond its role in the ER protein folding machinery and it acts at other cellular steps of host-pathogen interaction. PDI in the ER is also thought to play a role in parasite phagocytosis, and the PDI displayed on the cell surface can mediate the entry of some viral, bacterial, and protozoan. PDI is also implicated in protein unfolding and trafficking of some pathogenic antigens across the endoplasmic reticulum and towards the cytosol by the endoplasmic reticulum-associated degradation system (ERAD). This is the main pathway where proteins are retrotranslocated from the ER to cytosol and further degradated by the proteasome. Next, we discuss some examples of the cellular association between host PDI and different pathogens.

3.1. PDI and the Phagocytic Process

Phagocytosis is the main gate for large microbes to enter into APCs. After binding and attaching to the pathogen, these cells can internalize organisms and large particles even bigger then their own size, which are then phagocytosed in an active process that involves intense membrane remodelling [37]. Proteomics studies accumulated over the last decade revealed the presence of ER chaperones in the isolated phagosome, uncovering a process called ER-mediated phagocytosis [38–45]. ER chaperones were detected

in phagosomes of macrophages exposed to different particulate material and pathogens, including latex-beads opsonised or not with immunoglobulin G (IgG) or mouse serum (to facilitate entry through the FcR or complement receptors), IgG-opsonized erythrocytes, promastigotes of *Leishmania donovani* derived from wild-type cells or cell-surface LPG knockout, among other parasites [38]. A mix of ER and endocytic vesicles in the formation of the parasitophorous vacuoles (PVs) during the uptake of different *Leishmania spp*. was recently shown in macrophages overexpressing ER-tagged green fluorescent protein [41]. The presence of the ER proteins Sec61, Bip/Grp78, and PDI in the phagosome of APCs [38, 41] support the idea that the ER provides the necessary machinery for antigen translocation from the phagosome to the cytoplasm and thus, possibly converges MHC class I and class II antigen cross-presentation [42] (Figure 2). There are several other complementary hypotheses on how peptides cross from phagosomes to cytoplasm during the cross-presentation process [43, 44]. Neutrophils are short-lived cells (half-life of 4–8 h in the human circulation) and very active in the phagocytosis of large microbes such as bacteria, parasites, and fungus. Contrary to APCs, neutrophils only contain restricted amounts of ER machinery and are thought to lack the ER-mediated phagocytosis process [38].

Whether ER proteins functionally operate on phagocytosis-mediated infection has not been well characterised yet. An important work has shown that *Dictyostelium* lacking both ER calreticulin and calnexin present altered phagocytic cup formation and substantial decline in phagocytosis [45]. These two proteins utilise Ca, and their disruption per se affects actin filaments and plasma membrane remodelling during phagocytosis [45]. We recently showed that PDI is critically involved in *Leishmania* parasite infection in vitro [22]. We showed that phagocytosis of promastigotes (but not amastigotes) of *Leishmania chagasi* was significantly inhibited by macrophage incubation with the thiol/PDI inhibitors DTNB, bacitracin, phenylarsine oxide, and neutralizing PDI antibody in a parasite redox-dependent way [22]. The phenylarsine response is of particular interest, since this arsenic compound may act similarly to antimonials, widely used in leishmaniasis chemotherapy [46, 47]. PDI preferentially affects parasite internalization and the phagocytosis of the promastigote forms is increased when wild-type PDI is overexpressed in macrophages, an effect opposed by PDI knockdown. At later stages of infection (i.e., after 4 h), PDI from promastigote-infected J774 macrophages was immunoprecipitated and subsequently blotted with an anti-*Leishmania* antibody revealing a parasite band at $\sim$ 94 KDa [16, Figure 10(b), lane 5]. Subsequent removal and analysis of this band by mass fingerprint spectrometry showed a 58% match with elongation factor 2 (EF2) of L. major (Q4Q259; data not shown). The incubation of purified bovine PDI (Sigma, P3818) and parasites did not yield any detectable protein complexes, suggesting that the macrophage milieu may be important to sustain PDI-EF2 association [22]. Interestingly, *Leishmania* EF2 has important virulent features and acts as a soluble antigen in lymphocyte stimulation in vitro [48] and in vivo [49]. Moreover, proteomics studies revealed that EF2 is secreted during promastigote differentiation into the amastigote stage with potential immunomodulatory proprieties in animal models [50]. *Leishmania* EF2 is therefore of particular interest for *Leishmania* therapeutic interventions such as vaccines. Although our studies did not address the role of the ER in mediating phagocytosis, these data provide compelling evidence for a functional role of ER-PDI in a host-parasite interaction. Other mechanisms underlining PDI-mediated *L. chagasi* promastigote phagocytosis involves its association to ROS production by phagocyte NADPH oxidase and this is discussed next.

3.2. PDI and NADPH Oxidase Regulation

The NADPH oxidase (Nox) family of enzymes uses NADPH as an electron donor to convert oxygen to superoxide anion ($O_2^{\bullet -}$), a precursor of H_2O_2 and other powerful oxidants such as hydroxyl radical and peroxynitrite (in the presence of nitric oxide), collectively called ROS [3, 51, 52]. Each of the seven oxidase family members is characterized by a distinct catalytic subunit (i.e., Nox1-5 and Duox1-2), and has differing requirements for additional protein subunits [51, 52]. The prototypic member of the Nox family, Nox2 oxidase (or $gp91^{phox}$ oxidase), is best known for its role in neutrophil and macrophage phagocytosis. Genetic defects in the enzyme are related to chronic granulomatous disease, a condition in which affected children

suffer from recurrent severe fungal and bacterial infections due to defective phagocyte function [51]. Each Nox isoform forms heterodimers with a lower molecular weight $p22^{phox}$ subunit and is predicted to be membrane-bound. Nox2 is normally quiescent and acutely activated by agonists such as PMA, LPG, and cytokines in a tightly regulated process in which cytosolic subunits ($p47^{phox}$, $p67^{phox}$, $p40^{phox}$, and Rac1 in the case of macrophages and dendritic cells, or Rac2 in neutrophil) associate with the Nox2-$p22^{phox}$ heterodimer to initiate enzyme activity [51, 52]. Nox2 also has electrogenic features [53] and in APC cells is linked to the regulation of phagosome/lysosome pH and antigen processing [54, 55]. Usually, phagosome acidity is maintained by a vacuolar ATPase (V-ATPase) that transports protons from the cytosol into the phagosome lumen, therefore regulating the function of lysosome proteases in the fused phagolysosomes. Savina et al. [56–58] have shown that Nox2-derived superoxide in the phagosomal vesicle promptly consumes protons maintaining a higher pH ambient in dendritic cells during particle internalization, which favours antigen processing and presentation [56–58]. Opposite results were found in macrophages [56–58]. The selective role of Nox2 in different phagocytic cells remains to be defined. The jury is out on whether the results shown in macrophages (association of Nox2 to Rab27a; a member of Rab family of GTPases) are related to vesicle traffic molecule assembly and quality, or rather associated to degradation processes [59].

Nox complex protein expression and function is greatly affected by redox compounds, and it is especially regulated by PDI with implications for cell signalling [60]. The association of PDI to $p22^{phox}$ and other Nox isoforms in different cell types, especially in vascular cells, has been previously described [60–62]. A functional and spatial/physical interaction between PDI and the $p22^{phox}$ oxidase subunit was shown in macrophages [22] and more recently between PDI and $p47^{phox}$ in neutrophils [62]. In macrophages, PDI-Nox association was correlated to *Leishmania* infection in vitro [22]. It is well known that during phagocytosis of *Leishmania*, Nox2 is activated and parasite uptake is inhibited by antioxidants such as catalase [22]. Intriguingly, in the course of promastigote infection, some parasites evade that stressful condition and convert themselves into intracellular amastigotes, multiplying and resulting in progression to a disease process. Overall, our studies support the view that parasite phagocytosis/infection by macrophages is a redox process mediated by PDI in at least two ways. Initially, PDI-NADPH oxidase increases ROS production generating an oxidizing milieu, which seems to favour promastigote infection. The downstream role of ROS generated by PDI-NADPH oxidase remains unknown but can be related to the unfolded protein response signalling [63] or, similar to PDI-Ero1, to protein folding in the macrophage ER compartment with key implications for antigen processing. Nevertheless, at later stages of infection, macrophage PDI physically associates with *Leishmania* elongation factor-2 (as discussed earlier).

3.3. PDI Role on Cell Surface and Pathogen Attachment

Some viruses envelop their genetic material within a protein-coated capsid in a further lipid membrane layout, for example, influenza virus, baculovirus, hepatitis-C, HIV, and Herpes virus. These enveloped particles require successive steps to successfully entry and infect host cells. They usually first attach onto host receptors (and attachment factors), and their membranes fuse to interact with endosome vesicles that traffic the virus toward the endoplasmic reticulum, where it is uncoated. The proteins are finally transported to the cytosol and nucleus [64] (Figure 2). There is convincing evidence showing that most viral infections are strongly influenced by changes in the redox environment and that host PDI mediates infection of enveloped viruses [65–70].

In the course of HIV infection, the virus first binds to attachment factors, for example, mannose binding C-type lectin receptor and intracellular adhesion molecule (ICAM-3) on the surface of host $CD4^+$ T cells. The glycoprotein 120 (gp120) subunit of the virus envelope binds to immunoglobulin G of $CD4^+$ and undergoes conformational changes, allowing the virus to interact with its coreceptors, CXCR4 or CCR5. These interactions favour downstream conversions of gp41 envelope subunit to a competent fusion conformation. Initial studies showed that membrane-impermeable PDI inhibitors and monoclonal antibodies against PDI prevent HIV-1 infection [65]. It was then revealed that the domain D2 of the CD4 has redox-active disulfide bonds and is regulated by thioredoxin [66]. Using membrane-impermeable reducing

agents (especially arsenical-derived compounds) and labelling thiol reagents, it was demonstrated that $CD4^+$ reactive thiols critically drive HIV entry into cells [66]. Work from another group also revealed that PDI, on the surface of HIV-1 target cells, reduces disulfide bonds of the recombinant envelope glycoprotein gp120 (reaction 1, Figure 1), a reaction prevented by the usual PDI inhibitors [67]. Intriguingly, PDI silencing in U373 and HeLa cells had little impact on HIV infection itself as compared to the effect mediated by general thiol inhibitors [68]. The reasons for this discrepancy remain to be elucidated and raise the question whether the reductive effect of PDI is coupled to other redox proteins (e.g., thioredoxin or Nox's) that could amplify virus-CD4 redox association in some cells. It is noteworthy that in these later studies, PDI knockdown on the cell surface was not evident as compared to massive loss of most PDIs within the ER; an observation that supports the idea that PDI in the ER has little impact in HIV-mediated infection [68]. Thiol inhibitors also affect viral fusion as that mediated by the fusion (F) protein from the Paramyxovirus Newcastle disease virus [69]. The overexpression of PDI family members PFDI and ERdj5 has also been shown to significantly catalyze the reduction of thiols in F protein, facilitating membrane fusion [70]. There is evidence suggesting a possible association between PDI and infection mediated by some members of the of Herpesviridae viruses family [71].

PDI is also implicated in the attachment of some bacteria from different species of *Chlamydia* [72–74]. *Chlamydia* is an obligatory intracellular pathogen that causes diverse diseases in humans. The most common species are *Chlamydia trachomatis*, which is sexually transmitted and can cause blindness and infertility, and *C. pneumoniae*, which affects the respiratory tract. CHO cells have impaired endogenous PDI expression due to a defect in truncated mRNA processing, thus providing a valuable model to understand the effect of PDI-mediated cell-cell interaction and infection. These cells are very resistant to Chlamydia infection showing impaired attachment, an effect restored by ectopic expression of PDI [73]. Similar to HIV infection, the molecular mechanisms most likely include the reductive activity of PDI (reaction 1, Figure 1) on the surface of CHO cells [72].

3.4. PDI and Antigen Translocation from ER to Cytosol

Crossing the endoplasmic reticulum (ER) membrane is an irreversible process for most proteins. In some cases, however, this flow is reversed and misfolded proteins retained in the ER are retrotranslocated to the cytosol via ERAD to be degraded by the proteasome. This pathway is also exploited by small pathogens, especially non-enveloped viruses and some bacterial toxins, to gain access to the cytosol. In these cases, antigenic particles that reach the ER by different means suffer molecular redox rearrangements and binding to PDI allowing them to be transported back to the cytosol or nucleus. Well-known examples are infections mediated by Polyomaviruses (Py) and Simian virus 40 (SV40) extensively studied in the field of carcinogenesis. After SV40 interaction with the GM1 receptor on the cell surface, the particle enters the host cell through endocytosis and traffics via the caveosome (a particular caveolin containing endosome with neutral pH) towards the ER compartment [75, 76]. SV40-coated pentamers are linked to each other by disulfide bonds between cysteine 104 (C104). Further isomerisation in the ER is crucial for the viral uncoating process. In vitro cell screening shows that among all ER-resident proteins, PDI and ERp57 more specifically regulate SV40 infection [75]. PDI silencing substantially decreases SV40 infection that is also dependent on some redox sensitive cysteines on the viral particle [75]. PDI cooperation with ER-associated ERAD proteins Derlin-1 and Sel1L is Ca dependent and facilitates SV40 traffic through ERAD [75]. A similar pathway is used by some nonobligatory intracellular bacteria that exert their effect through production of potent endotoxins, such as diphtheria toxin (DT) and cholera toxin (CT). These proteins function similarly to some plant toxins, such as ricin and abrin. Conversion into toxic proteins involves cleavage of their interchain disulfide bond, allowing them to traffic into the endocytic pathway within the host cell [77, 78]. In humans, CT is derived from the *Bacterium Vibrio cholerae* that causes cholera disease and has 2 subunits (A1 and A2). The protein first attaches to the host cell surface via GM1 and the subunit A2, which contains a KDEL sequence, and is transported back to the ER (see earlier discussion). There, PDI reduces and unfolds A2 and A1 that exit the ER via the Sec61 channel into the cytosol. PDI in the

reduced state (reaction 1, Figure 1) binds to the toxin and subsequent oxidation of PDI, probably via Ero1α, enables the release of CT toxin [79, 80]. The active polypeptide A1 efficiently modifies a heterotrimeric G protein in the cytosol that leads to massive loss of chlorine and water secretion by intestinal epithelial cells in mammals, resulting in severe diarrhoea.

4. CONCLUSION

In this article we have reviewed the main cellular aspects of PDI-mediated host pathogen interactions and the pathways that are involved in viral, bacterial (including bacterial toxins), and parasitic infections. A number of cellular mechanisms through which PDI modulates some specific cellular pathways in immune cells have been described, such as redox-sensitive attachment, antigen presentation in the ER and exit from it, and association to phagosome and ROS production by NADPH oxidase (Figure 2). Many of these responses are antigen-specific and the precise mechanisms of action remain to be fully elucidated, especially in the context of redox changes in cross-presentation phenomena. Moreover, little is known about the role of PDI in infection per se, as well as how PDI signals to a more integrated cellular response to stress [63]. PDI global knockout mice are only viable until birth, but partial gene-modified mice and also modified pathogens will help to reveal the significant redox role of PDI and its redox partners. Overall, PDI is a key regulator that may propagate or limit the severity of the infection processes, depending on the infectious organism involved. A better understanding of these complex regulatory steps will provide insightful information on the redox role and coevolutional biological process, and assist the development of more specific therapeutic strategies in pathogen-mediated infections.

ABBREVIATIONS

ER: Endoplasmic reticulum
MHC: Major histocompatibility complex
H_2O_2: Hydrogen peroxide
ERp57: A member of PDI family also know as glucose-regulated protein or 58-kD (GRP58)
NF-kB: Factor nuclear kappa B
AP-1: Activator protein 1
STAT-3: Signal transducer and activator of transcription 3.

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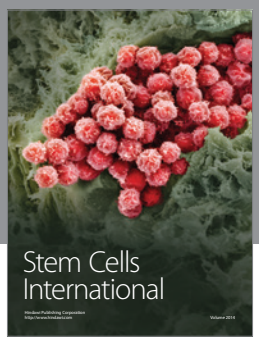

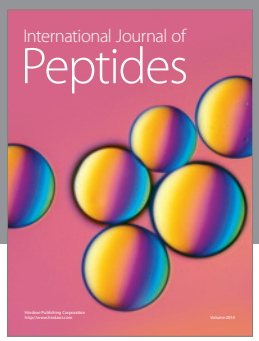

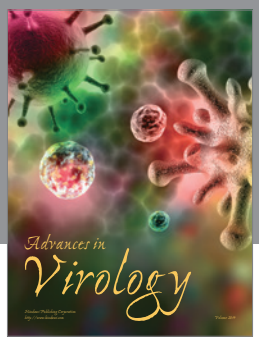

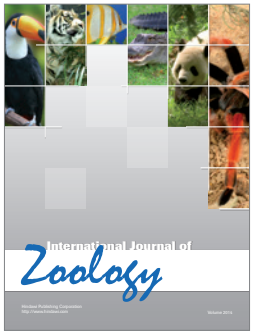

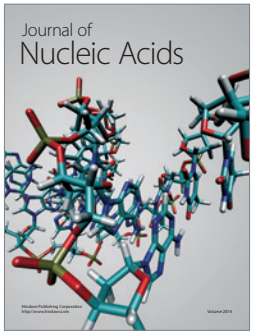

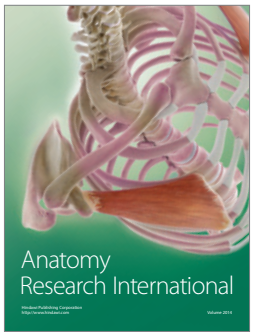

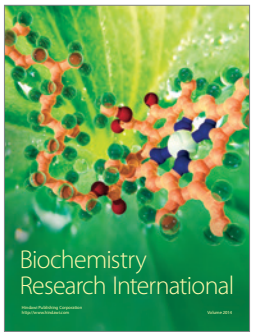

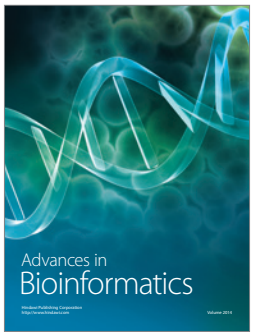

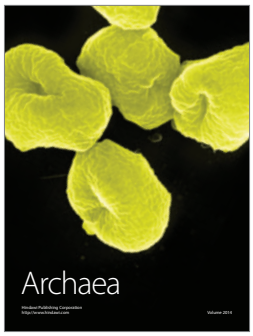

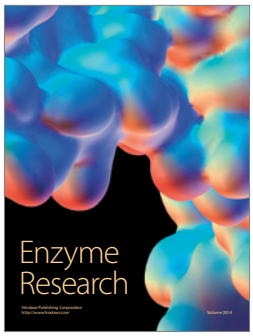

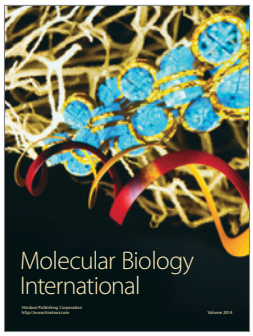

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