Members of the CD1 family of membrane glycoproteins can present antigenic lipids to T lymphocytes. Like major histocompatibility complex class I molecules, they form a heterodimeric complex of a heavy chain and β₂-microglobulin (β₂m) in the endoplasmic reticulum (ER). Binding of lipid antigens, however, takes place in endosomal compartments, similar to class II molecules, and on the plasma membrane. Unlike major histocompatibility complex class I or CD1b molecules, which need β₂m to exit the ER, CD1d can be expressed on the cell surface as either a free heavy chain or associated with β₂m. These differences led us to investigate early events of CD1d biosynthesis and maturation and the role of ER chaperones in its assembly. Here we show that CD1d associates in the ER with both calnexin and calreticulin in the context of the thiol oxidoreductase ERp57 in a manner dependent on glucose trimming of its N-linked glycans. Complete disulfide bond formation in the CD1d heavy chain was substantially impaired if the chaperone interactions were blocked by the glucosidase inhibitors castanospermine or N-butyldeoxynojirimycin. The formation of at least one of the disulfide bonds in the CD1d heavy chain is coupled to its glucose trimming-dependent association with ERp57, calnexin, and calreticulin.

CD1 molecules are transmembrane glycoproteins encoded by linked genes outside the major histocompatibility complex (MHC)I (reviewed in Ref. 1). The human CD1a, -b, and -c molecules constitute group I, whereas human and mouse CD1d molecules form group II. Like classical MHC class I and class II molecules, CD1d molecules are recognized by T cells. Certain αβ+ and γδ+ CD4-CD8- T cells were initially shown to lyse tumor cells expressing CD1a or CD1c (2). Subsequent studies showed that mycobacterial lipids, such as mycolic acids, lipoprotein, phosphatidylinositol (17, 18), to satisfy quality control mechanisms their egress from the ER. CD1d molecules may bind autologous lipids in the ER, such as phosphatidylinositol or glycosylphosphatidylinositol (17, 18), to satisfy quality control mechanisms and allow transport, before exchanging them in the endocytic pathway. Peptide binding by class I molecules is an essential requirement for their egress from the ER. CD1d molecules may bind autologous lipids in the ER, such as phosphatidylinositol or glycosylphosphatidylinositol (17, 18), to satisfy quality control mechanisms and allow transport, before exchanging them in the endocytic pathway for other autologous or foreign lipids.

Previous studies have examined the assembly of CD1 molecules. CD1b heavy chain was observed to bind calnexin and calreticulin in the ER and to require β₂m for subsequent transport to the cell surface (19, 20). In contrast, mouse and human CD1d molecules are expressed both as free heavy chains and as complexes with β₂m. This was observed not only in transfec- tants but also in primary tissue cells (21–23). CD1d expressed in β₂m-negative cells is fully capable of activating cognate T cells (23, 24), indicating that heterodimer formation may not be critical for CD1d function. Although a recent study showed that β₂m seems to modulate the structure of the heavy chain carbohydrates (22), the underlying mechanisms regulating CD1d expression with or without β₂m remain to be elucidated.

Here we present a detailed analysis of CD1d biosynthesis and an examination of the roles of ER chaperones in CD1d assembly. We show that CD1d heavy chains associate with calnexin, calreticulin, and the thiol oxidoreductase ERp57 and demonstrate a role for this association in the formation of CD1d heavy chain disulfide bonds.

MATERIALS AND METHODS

Cell Lines—The B-LCL C1R and .221, and their CD1d transfectants, were maintained in Iscove's medium (Invitrogen) containing 5% bovine calf serum or 10% fetal bovine serum at 37 °C.

Antibodies and Reagents—The mouse mAbs to human CD1d, 51.1.3 (22, 25, 26) and D5 (22, 26, 27), were gifts from Dr. S. Porcelli (Albert Einstein College of Medicine) and Dr. S. Balk (Harvard Medical School), respectively. The mAbs GAP.A3 (anti-HLA-A3 (28)), MaP.ERp57 (anti-ERp57 (29)), and HC10 (anti-class I (30)) have been previously described. The mAB AF8 (anti-calnexin (31)) was a gift from Dr. M. Brenner (Harvard Medical School). The rabbit anti-calreticulin serum and rat anti-Grp94 mAb were purchased from StressGen Biotechnologies Corp. (Victoria, BC, Canada) and anti-β₂m serum from Roche Applied Science (Indianapolis, IN). Dithiobis(succinimidylpropionate) (DSP) was purchased from Pierce and castanospermine (CST) from Applied Science (Indianapolis, IN). Dithiobis(succinimidylpropionate) (DSP) was purchased from Pierce and castanospermine (CST) from Applied Science (Indianapolis, IN).
Roche Applied Science. N-Butyldoxyojirimycin was a gift of Dr. K. Cannon (32).

Generation of Stable Transfectant Cell Lines—The vector CD1d/pSR-neo was a gift of Dr. S. Porcelli. C1R and .221 cells were transfected by electroporation at 230 and 210 V/960 microfarads, respectively. C1R.CD1d and .221.CD1d were selected for neomycin resistance at 1.8 and 0.6 mg/ml G418, respectively. C1R.CD1d and .221.CD1d were selected for neomycin resistance.

RESULTS

Assembly and Transport of CD1d Molecules—CD1d biosynthesis was examined in the B-LCL, C1R.CD1d, which is capable of activating CD1d-specific T cells (15). Cells were labeled with [35S]methionine/cysteine for 15 min and chased up to 20 h. They were lysed in 1% Triton X-100 and immunoprecipitated with mAbs 51.1.3 (anti-CD1d/βm) or D5 (anti-CD1d heavy chain). The immunoprecipitates were eluted by boiling in 0.2% SDS, 0.04 M sodium phosphate buffer, pH 6.5, and the supernatants were incubated with or without Endo H overnight before analysis by 12% SDS-PAGE. CD1d heavy chain (R, Endo H resistant; S, Endo H sensitive) and βm, Endo H resistant; and the supernatants were incubated with or without Endo H overnight before analysis by 12% SDS-PAGE. CD1d heavy chain as a percentage of total CD1d. C1R.CD1d (2 × 10^6 cells/lane, upper panels) and .221.CD1d cells (2 × 10^6 cells/lane, lower panels) were radiolabeled as in panel A. Cells were extracted in 1% Triton X-100 and immunoprecipitated with 51.1.3 (left panels) or rabbit anti-βm serum (right panels). CD1d heavy chains were SDS/DTT-eluted, reimmunoprecipitated with D5, incubated with or without Endo H, and analyzed by 12% SDS-PAGE.

Folding of Human CD1d Heavy Chain

**RESULTS**

**Assembly and Transport of CD1d Molecules**—CD1d biosynthesis was examined in the B-LCL, C1R.CD1d, which is capable of activating CD1d-specific T cells (15). Cells were labeled with [35S]methionine/cysteine for 15 min and chased up to 20 h. They were lysed in 1% Triton X-100 and immunoprecipitated with the anti-CD1d antibodies, 51.1.3 or D5, which recognize heavy chain-βm dimers and free heavy chains, respectively. Exit from the ER was monitored by loss of susceptibility to Endo H. Fig. 1 shows that the majority of Endo H-sensitive free heavy chains were converted to heavy chain-βm complexes within 2 h (Fig. 1B). Both βm-associated CD1d heavy chains and the residual free heavy chains underwent complex carbohydrate modification, manifested as smeared bands, starting at about 1 h for the heterodimer and 2–4 h for the free heavy chains. Concomitant loss of Endo H-sensitive bands indicates transport from the ER, and these results indicate that βm facilitates, but is not essential for, CD1d exit from the ER. That 51.1.3-recognizable CD1d is associated with βm was confirmed by comparing kinetics of maturation by immunoprecipitation with 51.1.3 and with anti-βm serum. The immunoprecipitates were eluted from the beads by boiling in 1% SDS/DTT/TBS, diluted in 1% Triton X-100/iodoacetamide/TBS, and the supernatants were reimmunoprecipitated with D5. Immunoprecipitation with either antibody showed identical CD1d transport kinetics in C1R.CD1d and in a second CD1d-expressing cell line, .221.CD1d (Fig. 1C).

To examine how fast CD1d heterodimers arrive at the cell surface, C1R.CD1d cells were radiolabeled for 15 min and...
chased up to 8 h. At each chase point, surface CD1d was captured by incubating the cells with the 51.1.3 mAb. Unbound 51.1.3 was removed by washing and the surface CD1d was isolated by adding protein G-Sepharose after lysis. The residual, mostly intracellular, CD1d was immunoprecipitated by adding additional 51.1.3 and protein G-Sepharose (Fig. 2A).

The immunoprecipitates were eluted from the beads, and released CD1d heavy chains were reimmunoprecipitated with the D5 mAb. The results showed that CD1d was detectable at the cell surface after 1 h and reached a plateau after 2.5 h (Fig. 2, B, upper panel, and C). The rate of transport to the cell surface was approximately the same as the rate of complex carbohydrate modification (Figs. 1 and 2B, lower panel). This suggests that the majority of newly synthesized CD1d is transported along the secretory pathway through the Golgi to the cell surface without detouring through endosomal compartments like class II molecules. Transport to the cell surface is not as rapid as seen for MHC class I molecules, but is faster than for MHC class II, a pattern very similar to that observed for CD1b (35). We observed similar surface transport kinetics by using a surface biotinylation technique (data not shown).

Association of CD1d with ER Chaperones—To determine whether the ER-resident proteins involved with the assembly of MHC class I molecules associate with CD1d, we performed co-immunoprecipitations in the detergent digitonin, conditions where their interactions with class I are maintained. Class I heavy chains bound calnexin, calreticulin, ERp57, the transporter associated with antigen processing (TAP), and tapasin, whereas CD1d associated only with the chaperones calnexin and calreticulin (data not shown). This is consistent with previous studies of TAP-deficient cells that showed that the class I peptide loading complex is not involved with CD1d assembly (36, 37). We also observed normal surface expression of CD1d in the tapasin-negative .220 B-LCL (38) transfected with CD1d (data not shown).

Calnexin and calreticulin are homologous lectin domain-containing ER chaperones that regulate glycoprotein folding in the ER by interacting with their N-linked glycans (reviewed in Ref. 39). After transfer to a protein two terminal glucose residues are removed from the glycan by glucosidase I. Glycoproteins bearing monoglucosylated N-linked glycans bind calnexin and calreticulin through their lectin domains and undergo folding and assembly. After release by the action of glucosidase II, which removes the terminal glucose, proper folding is monitored by the enzyme UDP-glucose:glycoprotein glucosyltransferase, which reglucosylates the N-linked glycans of nonnative structures. A correct conformation allows the glycoprotein to avoid reglucosylation and further interactions with calnexin and calreticulin. To determine whether calnexin and calreticulin association with CD1d is dependent on glucose trimming, radiolabeled C1R.CD1d cells were incubated with the glucosidase inhibitor CST for various times. Calnexin and calreticulin dissociation from CD1d was inhibited by CST, indicating that both interactions are glycan-dependent (data not shown).

Regulation of Disulfide Bond Formation in CD1d—Calnexin and calreticulin cooperate with the thiol oxidoreductase ERp57 to facilitate the formation or isomerization of disulfide bonds during glycoprotein folding (40–43). To investigate this for CD1d we first examined the redox state of CD1d heavy chains at various stages; the forms associated with calnexin or calre-
Folding of Human CD1d Heavy Chain

**Fig. 3. Oxidation states of CD1d associated with calnexin and calreticulin.** C1R.CD1d cells (3 × 10^6 cells/lane) were labeled with [35S]methionine/cysteine for 45 min, lysed in 1% digitonin, and immunoprecipitated with a control mAb GAPA3 (control, lanes 5 and 6), anti-calreticulin antibody (lanes 1 and 10), AF8 (anti-calnexin, lanes 2 and 9), 51.1.3 (anti-CD1d/β_m, lanes 3 and 7), or D5 (anti-CD1d heavy chain, lanes 4 and 8). The immunoprecipitates with AF8 and anti-calreticulin antibody were eluted in 1% SDS under nonreducing conditions, diluted in 1% Triton X-100, and CD1d heavy chains were reimmunoprecipitated with D5. All the immunoprecipitates were treated with Endo H overnight and analyzed by 12% SDS-PAGE under nonreducing (lanes 1–5) and reducing conditions (lanes 6–10). Fully reduced (Red), partially oxidized (Ox*), and fully oxidized (Ox) CD1d heavy chains are indicated.

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ticulin, the β_m-free, D5-reactive immature form, and the β_m-associated, 51.1.3-reactive mature form. C1R.CD1d cells were labeled for 45 min and extracts were immunoprecipitated with 51.1.3, D5, anti-calnexin, or anti-calreticulin antibodies. Antichaperone immunoprecipitates were eluted under nonreducing conditions (1% SDS and boiling), diluted in Triton X-100, and CD1d heavy chains were reimmunoprecipitated with D5. After treatment with Endo H to remove N-linked glycans and improve resolution, SDS-PAGE analysis showed that, whereas all forms of CD1d had identical mobilities under reducing conditions, there were differences under nonreducing conditions, reflecting differences in oxidation states (Fig. 3). β_m-associated CD1d heavy chains had the greatest mobility, i.e., were the most oxidized, whereas the calnexin- and calreticulin-associated forms and the D5-recognized form showed the same two bands. One is identical in mobility to the putatively fully oxidized, 51.1.3-recognized form, whereas the second is intermediate between that form and that seen upon complete reduction, consistent with only one of the internal disulfide bonds being oxidized.

**Glycosylation-dependent Interaction of Free CD1d Heavy Chains with Calnexin, Calreticulin, and ERp57—** We did not detect ERp57 association with CD1d under conditions that maintain the association between ERp57 and the class I loading complex (data not shown). However, detergents disrupt the interaction of ERp57 with most glycoproteins. We therefore used a cross-linking agent to preserve the interaction. C1R.CD1d cells were labeled for 45 min and lysed in 1% digitonin in the absence or presence of the reducible cross-linking agent, DSP (1 mM). The extracts were diluted in 1% Triton X-100 and immunoprecipitated with antibodies to ERp57, calnexin, calreticulin, and, as a negative control, Grp94. After elution in SDS, CD1d heavy chains were reimmunoprecipitated with the mAb D5 followed by reducing SDS-PAGE. The results show that CD1d remains associated with ERp57 only if cross-linker is added (Fig. 4A). The association of CD1d with calnexin and calreticulin was maintained in Triton X-100 without the cross-linker, and no interaction with Grp94 was observed regardless of the presence of the cross-linker.

By serial immunoprecipitation and SDS stripping, first with anti-ERp57 followed by anti-calnexin or anti-calreticulin and then by anti-CD1d, we also observed ternary complexes of ERp57, CD1d, and calnexin or calreticulin when the DSP cross-linker was used (Fig. 4B). To ask whether ERp57 association with CD1d is glucose trimming-dependent, C1R.CD1d cells were labeled for 45 min in the absence or presence of glucosidase inhibitors CST or N-butyldeoxynojirimycin. DSP cross-linked lysates were immunoprecipitated with antibodies against ERp57, calnexin, or calreticulin, SDS-eluted, and reimmunoprecipitated with the anti-CD1d antibody, D5. Analysis by SDS-PAGE showed that ERp57, together with calnexin and calreticulin, failed to associate with CD1d in the presence of the inhibitors (Fig. 4C). Previous reports indicate that ERp57 does not have lectin-like domains (41). These data, together with other reports (40, 44), indicate that CD1d associates with ERp57 indirectly via the lectin domains of calnexin or calreticulin.

During assembly of class I molecules newly synthesized free heavy chains associate with calnexin, whereas class I-β_m heterodimers associate with calreticulin (45). To determine whether this is the case for CD1d, C1R.CD1d cells were radiolabeled for 45 min, lysed in 1% digitonin, and the extract was immunoprecipitated with anti-β_m serum. β_m-associated molecules were competitively eluted with human β_m and reimmunoprecipitated with antibodies against calnexin and calreticulin. The associated CD1d was detected by immunoprecipitation with D5. The data show that, whereas class I-β_m dimers (HLA-C molecules in this case) were co-precipitated with calreticulin, CD1d-β_m dimers were co-precipitated with neither calnexin nor calreticulin (Fig. 4D). This indicates that both calnexin and calreticulin interact only with free CD1d heavy chains.

Because both calnexin and calreticulin associate with β_m-free CD1d heavy chain, and CD1d has four N-glycans,2 it seemed possible that CD1d heavy chain could form a ternary complex with both calnexin and calreticulin. This was tested by additional serial immunoprecipitation/stripping experiments on DSP cross-linked extracts. The results clearly show the existence of such a ternary complex (Fig. 4E). Given that both calnexin- and calreticulin-associated CD1d heavy chains are also associated with ERp57, the existence of a quaternary complex of CD1d, calnexin, calreticulin, and ERp57 seems likely.

The data suggest that disulfide bond formation in CD1d heavy chains is regulated by ERp57. Given that D5-reactive, calnexin-associated, and calreticulin-associated CD1d heavy chains show the same two bands on SDS-PAGE under nonreducing conditions (Fig. 3), we hypothesized that the D5-reactive partially oxidized form initially associates with calnexin, calreticulin, and ERp57 and that formation of the second disulfide bond occurs during association. If this is correct, inhibition of the CD1d-chaperone interaction should result in the accumulation of D5-reactive paracyctides (Fig. 5A). To test this, C1R.CD1d cells were radiolabeled for 5 min and chased in the absence or presence of CST. CD1d heavy chains were immunoprecipitated with D5, treated with Endo H, and subjected to nonreducing SDS-PAGE. The ratio of partially oxidized to fully oxidized heavy chains was indeed higher throughout the chase period in the presence of CST (Fig. 5, A and B).

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2 S.-J. Kang and P. Cresswell, unpublished observation.
A model of the early biogenesis of CD1d molecules based on the data presented here is depicted in Fig. 6. For simplicity only two of the N-linked glycans are shown. Calnexin and calreticulin simultaneously associate via monoglucosylated N-linked glycans with newly synthesized CD1d heavy chains in which one disulfide bond is already formed. Here we show the non-oxidized one as that in the α2 domain although there is no evidence to support this. Calnexin and/or calreticulin bring ERp57 to the β2m-free CD1d heavy chain and this mediates the formation of the second disulfide bond. The terminal glucose residues of the N-linked glycans are trimmed and the fully oxidized CD1d heavy chain then dissociates from the chaperones. The majority of the CD1d binds β2m but it can leave the ER even without it.

Useful comparisons can be made between the assembly path-
Folding of Human CD1d Heavy Chain

FIG. 5. Glucose trimming-dependent quality control determines the oxidation state of CD1d. A, C1R.CD1d cells (1.5 × 10⁶ cells/lane) were labeled for 5 min and chased in the absence or presence of 2 mM CST. CST was present during starvation, labeling, and chase periods. Cells were lysed in 1% Triton X-100, immunoprecipitated with D5 (anti-CD1d heavy chain), treated with Endo H, and analyzed by nonreducing (upper panel) or reducing (lower panel) 12% SDS-PAGE. As a control, extracts of cells (0.75 × 10⁶ cells/lane) continuously labeled for 45 min, without (lanes 1 and 2) or with (lanes 3 and 4) 2 mM CST, were also immunoprecipitated with D5 (lanes 1 and 3) or 51.1.3 (anti-CD1d/β₂m, lanes 2 and 4). Partially oxidized (Ox⁺) and fully oxidized (Ox) CD1d heavy chains are indicated. B, quantitation of the results in panel A presented as the ratio of partially oxidized and oxidized forms of CD1d heavy chain in the presence and absence of CST.

way illustrated in Fig. 6 and that of classical MHC class I molecules and even class II molecules. Both of these pathways involve calnexin, and class I assembly also involves calreticulin and Erp57. Class II molecules consist of heterodimers of transmembrane glycoproteins that associate with trimers of a third glycoprotein, the invariant chain, in the ER. Intermediates containing one or two αβ dimers bound to an invariant chain trimer remain associated with calnexin until the ultimate nonameric complex with three αβ dimers is complete (46). Whether Erp57 plays a role in this process is unknown. In class I assembly, newly synthesized heavy chains first bind calnexin. Calreticulin replaces calnexin when β₂m binds to the heavy chain, and, together with associated Erp57, this assembly is recruited to become part of a multisubunit “peptide loading complex” that also contains the heterodimeric TAP transporter and transmembrane glycoprotein tapasin (reviewed in Ref. 47). Recruitment of class I molecules to the loading complex requires calreticulin (48) and depends upon the generation of a monoglucosylated N-linked glycan in the class I heavy chain (40). Recently it has been shown that tapasin binds to Erp57 via an interchain disulfide bond, and cooperates with Erp57 in forming the correct disulfide bonds in the class I heavy chain (49). Formation of the loading complex, including calreticulin association (48) and tapasin-mediated Erp57 association, is required for proper peptide binding to class I molecules, and peptid binding is required for the class I-β₂m dimer to leave the ER (50, 51). Thus, this whole process can be understood as a unique quality control mechanism in which all the components, i.e. β₂m, calnexin, calreticulin, Erp57, TAP, tapasin, and even peptides, participate.

There are obviously significant differences between the CD1d and MHC class I assembly and transport pathways. First, β₂m association is not as critical for CD1d folding as it is for conventional class I molecules. Complete disulfide bond formation is achieved before β₂m associates with CD1d and β₂m-free CD1d heavy chain can leave the ER. This is further supported by previous studies, which showed that, even in vivo, β₂m is not critical for the function of CD1d. β₂m-free CD1d expressed in splenic cells from β₂m-deficient mice is fully capable of activating cognate T cells (23, 24). Second, the point in the assembly process where calreticulin interacts with MHC class I is different from that with CD1d. Class I associates with calreticulin only when complexed with β₂m, whereas CD1d associates with calreticulin as a free heavy chain. Moreover, CD1d can form a quaternary complex with calnexin, calreticulin, and Erp57. Calnexin and calreticulin may bind to different glycans of the CD1d heavy chain, similar to the situation with influenza virus hemagglutinin (52). How calnexin and calreticulin mediate the folding of CD1d heavy chain and which one is responsible for recruiting Erp57 remains to be elucidated.

Surface expression of CD1d in the calnexin-negative cell CEM.NKR is not impaired so calreticulin may be more critical for CD1d folding and assembly. Third, class I assembly may need to be tightly coupled to peptide loading because class I

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3 Radcliffe, C. M., Diedrich, G., Harvey, D. J., Dwek, R. A., Cresswell, P., and Rudd, P. M. (2002) J. Biol. Chem. 277, 46415–46423.

4 S.-J. Kang and P. Cresswell, unpublished data.
must survey the available peptides in the ER and optimize the associated repertoire. Quality control of CD1d may not need to be tightly coupled to optimal lipid binding in the ER, although lipids may bind there (see below), because it samples antigenic lipids in the endocytic pathway. In other words, optimization of antigen binding may be separable from quality control, being restricted to the place where antigen presenting molecules survey antigens. This is further substantiated by studies of class Ib molecules, H2-M3, HLA-E, and Qa-1. These are structurally similar to class I molecules but bind hydrophobic peptides, N-formylated peptides, or signal peptides of class Ia molecules, respectively. When their cognate peptides are not available, they are retained in the ER (53–58). Similarly, the stability of class II molecules is determined by peptide exchange mediated in the endocytic pathway by DM molecules.

Given the hydrophobic nature of the CD1d binding groove it seems unlikely that the CD1d molecule would satisfy ER quality control mechanisms, and avoid reglucosylation of one or more of its N-linked glycans by UDP-glucose:glycoprotein glucosyltransferase, unless the groove is occupied. As already discussed, the binding site of class I molecules must be occupied by peptides, and the peptide binding site of MHC class II molecules also must be occupied for efficient transport from the ER, in this case by the CLIP region of the invariant chain. For the CD1d family, ER-derived lipids, such as the phosphatidylinositol and glycosphingolipid-inositol associated with soluble, secreted mouse CD1d, are the likely occupants of the binding groove in the ER (17, 18).

Acknowledgment—We thank Nancy Domieten for help with preparation of this manuscript.

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Folding of Human CD1d Heavy Chain
Calnexin, Calreticulin, and ERp57 Cooperate in Disulfide Bond Formation in Human CD1d Heavy Chain
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J. Biol. Chem. 2002, 277:44838-44844.
doi: 10.1074/jbc.M207831200 originally published online September 17, 2002

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