Mini-review

Cell Stress & Chaperones (2003) **8** (4), 303–308
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Article no. csac. 2003.465

CHIP: a link between the chaperone and proteasome systems

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Abstract CHIP, carboxy terminus of Hsc70 interacting protein, is a cytoplasmic protein whose amino acid sequence is highly conserved across species. It is most highly expressed in cardiac and skeletal muscle and brain. The primary amino acid sequence is characterized by 3 domains, a tetratricopeptide repeat (TPR) domain at its amino terminus, a U-box domain at its carboxy terminus, and an intervening charged domain. CHIP interacts with the molecular chaperones Hsc70-Hsp70 and Hsp90 through its TPR domain, whereas its U-box domain contains its E3 ubiquitin ligase activity. Its interaction with these molecular chaperones results in client substrate ubiquitylation and degradation by the proteasome. Thus, CHIP acts to tilt the folding-refolding machinery toward the degradative pathway, and it serves as a link between the two. Because protein degradation is required for healthy cellular function, CHIP's ability to degrade proteins that are the signature of disease, eg, ErbB2 in breast and ovarian cancers, could prove to be a point of therapeutic intervention.

INTRODUCTION

Proper protein folding is essential for optimum protein performance and normal cellular function. The molecular chaperones check and enable correct folding of nascent polypeptides. By binding to exposed hydrophobic regions, they allow or promote proper folding and the correct tertiary conformation. They are also required for protein ''refolding'' because proteins denature because of age, stress, disease, and gene mutation.

During synthesis of new proteins and refolding of denatured proteins, cooperation between the cell's molecular chaperones and its degradation machinery must occur because some proteins cannot attain their correct tertiary conformation spontaneously. The mutually exclusive pathways of folding and degradation constitute the cell's protein quality control system. The choice between the 2 pathways has come to be known as ''molecular triage'' (Wickner et al 1999). The factors that influence this molecular triage decision are not clearly understood. Difficulty with folding and, therefore, the time spent in a partially folded conformation can influence the pathway chosen. Other factors—such as age, disease, or stress—can affect the fraction of unfolded proteins and, consequently, can affect the balance of protein ''rescue'' or protein degradation. Whether this decision is a stochastic process or a regulated and ordered process is also not clear.

To understand this issue, one benefits from looking at the class of proteins called ''molecular cochaperones.'' This ever-growing clutch of proteins interacts directly with chaperones such as Hsc70 and Hsp90 and modulates their functions. The J-domain proteins such as Hsp40 are prototypical cochaperones that interact with Hsc70 and enhance adenosine triphosphatase (ATPase) activity and folding reactions, and more recently, cochaperones with other functions (such as conformational stabilization and nucleotide exchange) have been identified. Recent evidence indicates that another cochaperone, CHIP (carboxyl terminus of Hsc70 interacting protein), also regulates chaperone function in part by regulating the molecular triage decision and determining whether proteins enter the productive folding pathway or the degradation pathway.

Characterization of CHIP

Proteins containing tetratricopeptide repeat (TPR) domains are involved in many protein-protein interactions (Lamb et al 1995); in particular, several heat shock protein interaction partners—including Hip, Hop, and the cyclo-

Received 28 May 2003; Accepted 29 May 2003.
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philins—interact with Hsc70 or Hsp90 through TPR domains (Ratajczak et al 1993; Hohfeld et al 1995; Demand et al 1998). In an attempt to identify additional proteins that might be involved in stress regulation, a human heart complementary deoxyribonucleic acid (cDNA) library was screened with a fragment of cyclophilin-40 containing its 3 carboxy-terminal TPR domains (Ballinger et al 1999). CHIP was identified through this screen. The CHIP cDNA encodes a 34.5-kDa protein containing three 34-amino acid TPR domains at its amino terminus (Ballinger et al 1999) and a ''U-box'' domain at its carboxyl terminus (Murata et al 2001). U-box domains are similar to RING finger domains, but they lack the metal-chelating residues and are thought to be structured by intramolecular interactions (Aravind and Koonin 2000). The predicted structural similarity between RING fingers and U-box domains suggests that U boxes, like RING fingers, may also play a role in targeting proteins for ubiquitylation and subsequent proteasome-dependent degradation. Separating the TPR and U-box domains in CHIP is a central domain rich in charged residues and also containing 2 possible nuclear localizing signals. The function of CHIP's charged domain is not yet known, although it is necessary for TPR-dependent interactions (Ballinger et al 1999). Comparison of the amino acid sequence of CHIP across species indicates that human CHIP shares 98% amino acid similarity with mouse and 60% similarity with Drosophila (Ballinger et al 1999). Strikingly, the most highly conserved region is in the 94 residues at the carboxyl terminus, the U-box domain, with 87% similarity among these species (Ballinger et al 1999).

The messenger ribonucleic acid (mRNA) tissue distribution of CHIP by Northern blot analysis supports the notion that it participates in protein folding and degradation decisions, because it is most highly expressed in tissues with high metabolic activity and protein turnover: skeletal muscle, heart, and brain. Although it is also present in all other organs, including pancreas, lung, liver, placenta, and kidney, the expression levels are much lower. CHIP mRNA can also be detected in most cell lines and in primary cell cultures (Ballinger et al 1999). Intracellularly, CHIP is primarily localized to the cytoplasm under quiescent conditions (Ballinger et al 1999), although a fraction of CHIP is present in the nucleus (Meacham et al 2001). Our observations indicate that CHIP may undergo intracellular trafficking in response to environmental challenge in cultured cells, the consequence of which is not yet certain (McDonough and Patterson, unpublished observations).

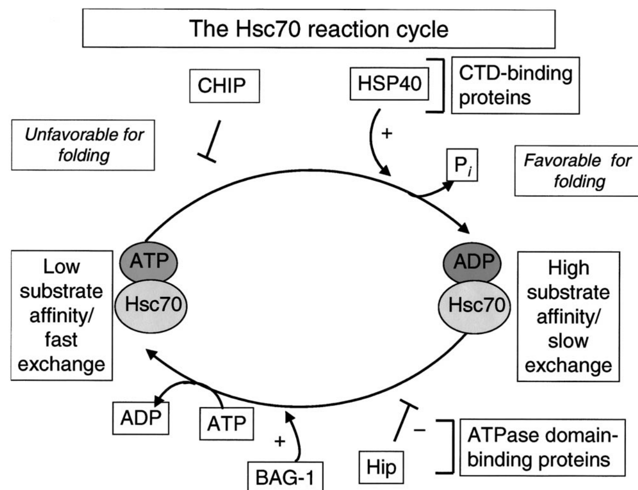

Fig 1. The Hsc70 reaction cycle. This diagram depicts the relationship between Hsc70, its cochaperones, and nucleotide-dependent folding properties of Hsc70.

CHIP interactions with the molecular chaperones Hsc/Hsp70 and Hsp90

Further characterization of CHIP led to the discovery that CHIP is a bona fide interaction partner with the major cytoplasmic chaperones Hsc70 and Hsp70, based on their interactions with CHIP in a yeast 2-hybrid screen and in vitro binding assays (Ballinger et al 1999). The binding determinants required for CHIP's interactions with Hsc70 have been mapped using glutathione S-transferase (GST) fusion protein assays. The TPR domain and an adjacent charged region of CHIP (amino terminus residues 1 to 197) are necessary for its interaction with Hsp70 and Hsc70 (Ballinger et al 1999), and CHIP interacts with the carboxy-terminal domain of Hsc70 (residues 540 to 650 of Hsc70), which is known to contain a TPR-acceptor site that also interacts with the TPR domain-containing cochaperone HOP (Demand et al 1998).

Although the carboxy-terminal domain of the 70-kDa heat shock proteins is the interaction domain for CHIP's amino terminal TPR domain, it is the amino terminal ATP-binding domain of Hsp70-Hsc70 that regulates substrate binding in a nucleotide-dependent fashion. The molecular cochaperones Hip and Hsp40 promote substrate binding by stabilizing the adenosine diphosphate (ADP)-bound conformation and activating ATPase activity, respectively (Hohfeld et al 1995; Minami et al 1996), whereas BAG-1 promotes substrate release by exchanging ATP for ADP (Hohfeld and Jentsch 1997) (Fig 1). In contrast, CHIP inhibits ATP hydrolysis and, therefore, attenuates substrate binding and refolding, resulting in inhibition of the ''forward'' Hsp70-Hsc70 substrate folding-refolding pathway, at least in in vitro assays. The cellular consequences of this ''antichaperone'' function are not yet clear. This activity may provide a mechanism to slow the Hsc70 reaction cycle under stressful conditions, or it may assist in ''loading'' misfolded proteins into the ubiquitin-proteasome machinery, as described below.

Because Hsp90 also contains a TPR-acceptor site to in-

teract with cochaperones, the possibility that CHIP might also interact with Hsp90 has been entertained (although seldom do TPR-containing proteins interact with both the Hsp90 and Hsp70 family of chaperones). Indeed, CHIP does interact with Hsp90 with approximately equivalent affinity to its interactions with Hsp70 (Connell et al 2001). This interaction results in remodeling of Hsp90 chaperone complexes, such that the cochaperone p23 (which is required for the appropriate activation of several Hsp90-dependent steroid receptors such as the glucocorticoid receptor [GR]) is excluded. The mechanism for this activity is unclear—p23 and CHIP bind Hsp90 through different sites—yet, the consequence of this action is predictable: CHIP should inhibit the function of proteins that require Hsp90 for conformational activation. The GR is an Hsp90 client that undergoes activation through a well-described sequence of events that depend on interactions of the GR with Hsp90 and various Hsp90 cochaperones, including p23, making it an excellent model to test this prediction. Indeed, CHIP inhibits GR substrate binding and steroid-dependent transactivation ability. Surprisingly, this effect of CHIP is accompanied by decreased steady-state levels of GR, and CHIP induces ubiquitylation of the GR in vivo and in vitro and proteasome-dependent degradation. This effect is both U box– and TPR-domain dependent, suggesting that CHIP's effects on GR require direct interaction with Hsp90 and direct ubiquitylation of GR and delivery to the proteasome.

These observations are not limited to the GR. ErbB2, another Hsp90 client, is also degraded by CHIP in a proteasome-dependent fashion (Xu et al 2002). Nor are they limited to Hsp90 clients; the cystic fibrosis transmembrane conductance receptor, an Hsp70 client, undergoes CHIP-dependent degradation that is Hsp70 dependent (Meacham et al 2001), and luciferase undergoes CHIP-dependent ubiquitylation in vitro when it is misfolded and bound by Hsp70 (Murata et al 2001). In each case, the effects of CHIP are dependent on both the TPR domain, indicating a necessity for interactions with molecular chaperones, and the U box, which suggests that the U box is most likely the ''business end'' with respect to ubiquitylation.

The means by which CHIP-dependent ubiquitylation occurs is not clear. In the case of ErbB2, ubiquitylation depends on a transfer of the client protein from Hsp90 to Hsp70 (Xu et al 2002), indicating that the final ubiquitylation complex consists of CHIP, Hsp70 (but not Hsp90), and the client protein. In any event, the studies are consistent in supporting a role for CHIP as a key component of the chaperone-dependent quality control mechanism. CHIP efficiently targets client proteins, particularly when they are partially unfolded (as is the case for most Hsp90 clients when bound to the chaperone) or frankly misfolded (as is the case for most proteins binding to Hsp70 through exposed hydrophobic residues).

CHIP is a prototypical U box with ubiquitin ligase activity

Once the ubiquitylation activity of CHIP was recognized, it was logical to speculate that its U box might function in a manner analogous to that of RING fingers, which have been appreciated rather recently as key components of the largest family of ubiquitin ligases. The ubiquitylation reaction in vivo requires, in addition to ubiquitin itself: a ubiquitin-activating enzyme (or E1), which forms a thiolester bond with ubiquitin at its carboxyl terminus; a ubiquitin-conjugating enzyme (or E2), which accepts activated ubiquitin from E1; and a ubiquitin ligase, or E3, which forms a complex with E2 and substrate to catalyze the transfer of ubiquitin residues, which generally are added progressively to substrates until the multiubiquitin chains are long enough to target the substrate to the proteasome for degradation (Hershko and Ciechanover 1998; Jackson et al 2000). If CHIP is a ubiquitin ligase, then its ability to ubiquitylate a substrate should be reconstituted in vitro, when a substrate is added in the presence of CHIP, E1, an E2, and ubiquitin. Indeed, this is the case (Jiang et al 2001; Murata et al 2001). CHIP is thus the first described chaperone-associated E3 ligase. The ubiquitin ligase activity of CHIP depends on functional and physical interactions with a specific family of E2 enzymes, the UBC4/UBC5 family, which in humans comprises the E2s UBCH5a, UBCH5b, and UBCH5c (Jiang et al 2001; Murata et al 2001). Of interest is the fact that the UBC4/UBC5 family of E2s is ''stress-activated'' ubiquitin-conjugating enzymes (Seufert and Jentsch 1990). CHIP can therefore be seen as a cochaperone that, in addition to inhibiting traditional chaperone activity, converts chaperone complexes into a chaperone-dependent ubiquitin ligase. Evidence that CHIP directly identifies and associates with misfolded proteins has not been forthcoming, thus the most likely model (yet to be tested formally) is that the chaperones themselves are the substrate-recognition components of these ubiquitin ligase complexes, with the chaperones functioning as ''F-box equivalents,'' analogous to many RING finger-containing ubiquitin ligase complexes that require an F-box-containing protein as the substrate-recognition module (Jackson et al 2000; Jackson and Eldridge 2002).

An escort to the proteasome

Although multiubiquitylation of substrates is the classic signal for proteasome-dependent degradation, there still remains the issue of how these substrates are transported to the proteasome. Several lines of evidence suggest that

CHIP participates in substrate ''delivery'' to the proteasome: (1) CHIP interacts with the S5a proteasome subunit in yeast 2-hybrid and GST pulldown assays, (2) the HC8 particle of the proteasome is detected in CHIP immunoprecipitates in vivo, and (3) CHIP colocalizes with the proteasome in cells treated with proteasome inhibitors (Connell et al 2001; Meacham et al 2001). These data provide further support for the model that CHIP is a molecular link between the cellular folding-refolding machinery and the cellular degradation machinery and suggest that CHIP may also participate in the transport of ubiquitylated proteins to the proteasome for their degradation.

Interestingly, the cochaperone BAG-1 has also been implicated in transport to the proteasome (Luders et al 2000). BAG-1 associates with the proteasome through its amino terminal ubiquitin-like domain and it binds to the proteasome in an ATP-dependent manner (Luders et al 2000). In the case of CHIP, the mechanism of proteasome association remains enigmatic but probably involves its E3 ubiquitin ligase activity. In addition to catalyzing ubiquitylation of Hsp/Hsc70 and Hsp90 substrates, CHIP also ubiquitylates Hsc70 with short noncanonical multiubiquitin chains and autoubiquitylates itself (Hatakeyama et al 2001; Jiang et al 2001). The ubiquitylation of Hsc70 and of CHIP itself does not serve as a signal for degradation (Jiang et al 2001). One possible function of such noncanonical ubiquitylation may be to target Hsc70 and CHIP, along with their cargo substrates, to the proteasome. Interestingly BAG-1 and CHIP may function as partners in delivering substrates to the proteasome. A direct interaction between the 2 cochaperones is indicated by the finding that BAG-1 and CHIP coprecipitate, and the addition of Hsc70 increases the amount of CHIP in these immunocomplexes (Demand et al 2001). Although overexpression of BAG-1 alone does not increase the rate of turnover of a model chaperone substrate (the GR), coexpression of BAG-1 with CHIP does increase its degradation, suggesting that the physical interaction between BAG-1 and CHIP is cooperative with respect to targeting chaperone substrates for degradation. The model suggested by these studies is that the proteasome binding activity of BAG-1 (through its ubiquitin-like domain) and its stimulation of substrate release from Hsc/Hsp70 can act in concert with CHIP's ubiquitin ligase activity to deliver substrates to the proteasome such that they will be recognized as marked for degradation (Demand et al 2001). Thus, cooperation between 2 Hsc/Hsp 70 molecular cochaperones tilts the molecular folding-refolding machinery toward the degradation pathway with CHIP's multiubiquitylation activity providing the rate-limiting step.

Protein folding-degradation machinery and disease

The elucidation of CHIP's roles in the cell has helped clarify the mechanism of linkage between the cells protein folding-refolding machinery and its degradation machinery—the 2 pathways called upon to provide protein quality control in the cell and thereby maintain healthy cellular function, particularly in the setting of cellular stress. Characterization of CHIP function may therefore provide insights into how the cellular processes contribute to physiologic and pathologic processes at the cellular and organismal level. Although a link with CHIP and pathophysiologic states is largely speculative at present, it is worth considering how the basic observations of CHIP at the level of biochemistry and cell biology can provide clues to understanding human disease.

For example, further clarification of the factors that push the protein quality control machinery down one pathway or the other may help in understanding the possible failures in this system that result in the accumulation of misfolded protein aggregates that are the signature of several degenerative disease states, such as the Lewy bodies in Parkinson disease, the neurofibrillary tangles in Alzheimer disease, and the ubiquitin-positive inclusions in polyglutamine-repeat diseases. In fact, recent data provide a direct link between CHIP and the pathophysiology of Parkinson disease. In juvenile Parkinson disease, mutations in the Parkin gene result in loss of dopaminergic neurons and the consequent motor deficits associated with Parkinson disease. Parkin is a RING finger E3 ubiquitin ligase, and PaelR (the membrane receptor for Pael) is 1 well-characterized substrate for its E3 activity. The accumulation of PaelR when Parkin is mutated is thought to contribute to the pathology of Parkinson disease. The degradation of unfolded PaelR by Parkin requires the participation of CHIP. CHIP promotes release of PaelR from Hsc/Hsp 70, and only upon this release can Parkin act as a ubiquitin ligase to signal PaelR degradation (Imai et al 2002). Although it is not entirely clear from the biochemical data available how the respective ubiquitin ligase activities of CHIP and Parkin cooperate to trigger ubiquitylation of substrates in this context, the 2 proteins have cooperative effects in protection against neuronal cell death. In any event, these results indicate that CHIP has a direct role in a particular protein quality control pathway that results in a neurodegenerative disease when it is impaired.

As a key player in eliminating damaged or unneeded proteins, one can imagine that CHIP may also have protective functions in other cell types and organs that are susceptible to chronic stress. For example, the high levels of CHIP expressed in the heart (Ballinger et al 1999) may reflect the ''wear and tear'' on cardiac tissue that is constant and for which protein turnover and degradation is

a continual requirement. The pathology of alphaB crystallin accumulation is a case in point. Specific mutations in the alphaB crystallin gene result in its misfolding, which overwhelms chaperone activity within cardiomyocytes leading to accumulation within the cell and a dilated cardiomyopathy. Congestive heart failure and lethal arrhythmias are the consequence of accumulation of alphaB crystallin deposits (Vicart et al 1998). This is one obvious example of how failure of protein quality control leads to cardiac dysfunction. It will be interesting to determine whether this is a more general mechanism of cardiac dysfunction, and the extent to which proteins such as CHIP may play a protective role in this setting.

Beyond its function of eliminating damaged proteins, CHIP's ubiquitylating activity could also serve to mark proteins for degradation because they are no longer needed for a specific cellular function, such as a signaling event. The identification of the signaling molecule ErbB2 as a CHIP substrate provides an example of this type of regulation (Xu et al 2002). ErbB2 overexpression is linked to an aggressive outcome in human breast cancers, and strategies to target ErbB2 degradation through activation of chaperone-dependent pathways involving CHIP may have therapeutic potential (Citri et al 2002). These observations should inspire further work linking CHIP substrates with specific cellular functions in situations where chaperone-dependent protein degradation plays a critical role.

Summary

As our understanding of the biochemistry of molecular chaperones and cochaperones improves, the mechanisms of their involvement in protein homeostasis and in pathways that promote and protect cellular health will serve to present potential points of intervention to prevent or improve diseased states. CHIP, as a cochaperone linking the folding-refolding and degradation pathways and as a potential cellular stress capacitor, could prove to be a pivotal player in these processes.

ACKNOWLEDGMENTS

Work in the Patterson laboratory is supported by NIH grants HL61656, GM61728, HL65619, AG21096, and HL072347 (to C.P.). C.P. is an Established Investigator of the American Heart Association and a Burroughs-Wellcome Clinical Scientist in Translational Research.

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