Genes & Diseases (2022) 9, 1521–1555

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journal homepage: http://ees.elsevier.com/gendis/default.asp

REVIEW ARTICLE

Chaperone-assisted E3 ligase CHIP: A double agent in cancer

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Received 25 May 2021; accepted 6 August 2021
Available online 1 September 2021

KEYWORDS
Chaperones (HSC70/HSP70 & HSP90);
CHIP;
Oncogene;
Therapy;
Tumor suppressor;
Ubiquitin proteasome system (UPS)

Abstract The carboxy-terminus of Hsp70-interacting protein (CHIP) is a ubiquitin ligase and co-chaperone belonging to Ubox family that plays a crucial role in the maintenance of cellular homeostasis by switching the equilibrium of the folding-refolding mechanism towards the proteasomal or lysosomal degradation pathway. It links molecular chaperones *viz*. HSC70, HSP70 and HSP90 with ubiquitin proteasome system (UPS), acting as a quality control system. CHIP contains charged domain in between N-terminal tetratricopeptide repeat (TPR) and C-terminal Ubox domain. TPR domain interacts with the aberrant client proteins *via* chaperones while Ubox domain facilitates the ubiquitin transfer to the client proteins for ubiquitination. Thus, CHIP is a classic molecule that executes ubiquitination for degradation of client proteins. Further, CHIP has been found to be indulged in cellular differentiation, proliferation, metastasis and tumorigenesis. Additionally, CHIP can play its dual role as a tumor suppressor as well as an oncogene in numerous malignancies, thus acting as a double agent. Here, in this review, we have reported almost all substrates of CHIP established till date and classified them according to the hallmarks of cancer. In addition, we discussed about its architectural alignment, tissue specific expression, sub-cellular localization, folding-refolding mechanisms of client proteins, E4 ligase activity, normal physiological roles, as well as involvement in various diseases and tumor biology. Further, we aim to discuss its importance in HSP90 inhibitors mediated cancer therapy. Thus, this report concludes that CHIP may be a promising and worthy drug target towards pharmaceutical industry for drug development.

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Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2021.08.003

Introduction

The functional state of proteins changes into malfunctioned state that results in serious ailments related to neurological, immune, cardiovascular systems and so on. As a prevention to these ailments, proteome will try to maintain the cellular homeostasis by two ways: (a) *via* proteasomal abasement of malfunctioned polypeptides and (b) *via* molecular chaperones mediated refolding. Cellular homeostasis is well maintained by proper balance between molecular chaperones and degradation machinery. Proteasome mediated abasement of malfunctioned polypeptides occur through ubiquitin proteasome system (UPS) or autophagy, which may works in an independent as well as synergistic manner.[1,2] On the other hand, molecular chaperone (like HSP70, HSP90 etc.) behaves like an inspector that inspects and guides the folding machinery of proteome to recycle the malfunctioned polypeptides into their native form. Furthermore, molecular chaperones also assist the proteasome mediated degradation machinery along with their role in refolding machinery.[3,4]

UPS is a multi-component system that regulates cellular threshold of malfunctioned and misfolded proteins or polypeptide through degradation in some bacteria,[5] all eukaryotic cells,[6–10] and archaea.[11] Proteasome mediated protein degradation is catalyzed by series of enzymatic reactions. UPS involves three well known enzymes *viz* ubiquitin activating enzymes (E1s), ubiquitin conjugating enzymes (E2s) and ubiquitin ligase enzymes (E3s) (Fig. 1).[12] The fourth one is known as ubiquitin chain elongating enzymes (E4s) that also found in UPS mediated degradation machinery.[13] Ubiquitin (~8.5 kDa protein)[14–16] is activated and conjugated to the E2 enzyme in the presence of ATP and E1 enzyme.[17] Next, E2-ubiquitin complex[18] is catalyzed in the presence of E3 ubiquitin ligases and transferred the ubiquitin molecule to the client protein. Peptide bonds are formed between specific lysine residues of client proteins and glycine residue in the carboxy terminus of ubiquitin molecule.[19,20] E4 type of enzymes are also involved in the degradation machinery of UPS, responsible for polyubiquitination of client proteins. Seven types of ubiquitin lysine residues (K6, K11, K27, K29, K33, K48 and K63) are responsible for polyubiquitination. Polyubiquitinated client proteins are transferred and degraded by 26s proteasome.[21] Secondly, autophagy is another system of maintaining homeostasis of proteome by lysosome mediated proteolysis. Cellular abnormal proteins are automatically engulfed by phagosome called autophagosome. Autophagosome is further engulfed by a lysosome complex, called auto-phagolysosome and is ultimately degraded through lysosomal hydrolysis.[22] Furthermore, chaperones are also involved in lysosome mediated proteolysis *viz*, chaperone assisted selective autophagy (CASA) and chaperone-mediated autophagy (CMA).[22–24] Over 500 E3 ligases are identified till date,[25] here in this report, we are presenting an overview of up-to-date information of CHIP with special attention to its dual role in cancer and possible strategy for combinatorial use with HSP90 inhibitors.

CHIP: discovery, gene location, mutations, architectural alignment, tissues specific expression and sub-cellular localization

CHIP is playing important and selective role in the proteolysis of its client proteins through UPS. It is responsible for its dual action as a co-chaperone and an E3 ligase. It plays a major role in maintaining tissue homeostasis through maintenance of cellular threshold of client proteins including oncogenes and tumor suppressors by UPS/lysosomal degradation.[26,27] In this section, we are providing a brief overview into its discovery, gene location, mutations, architectural alignment, tissues specific expression and its sub-cellular localization.

Discovery

Tetratricopeptide repeat (TPR) domain of CHIP is a key element responsible for protein–protein interactions. Based upon this fact Ballinger and his colleagues tried to find out the novel interacting proteins of TPR domain. Therefore, his team had started and successfully screened the human heart cDNA library with a fraction of cyclophilin-40 containing three TPR repeats. Through this screening, CHIP (a 34.8 kDa encoded protein) containing three TPR repeats at its N-terminus with Ubox domain at C-terminus was identified.[28–30] Furthermore, amino acid arrangements of human CHIP have similarity with ~98% of mouse CHIP and ~60% of fruit fly CHIP. Surprisingly, Ubox domain regions of all three species have 87% amino acid similarity which indicates that 94 amino acid residues of Ubox domain of these species are similar and found to be highly conserved.[31]

Gene location and mutations

Protein CHIP is encoded by gene *STUB1* (STIP1 homology and U-box containing gene-1) which is located at p13.3 in chromosome number 16. In humans, it consists of 7 exons and 6 introns and translated into 303 amino acid containing protein.[28] Till date, two isoforms of human CHIP containing 303 & 231 amino acids are reported with Uniprot IDs Q9UNE7-1 and Q9UNE7-2 respectively; but no experimental proofs are available for second isoform.

Mutations are the changes in DNA sequence that can occur during copying of DNA or may be induced by some environmental factors (*viz.*, UV light, smoking, chemical reagents etc.) that can produce serious illness.[32,33] Recent reports state that *STUB1* gene mutations are associated with various major diseases like Gorden Holmes syndrome (GHS),[34,35] Machado-Joseph disease (MJD)[36,37] and intracranial aneurysm (IA).[38] GHS is characterized by hereditary cerebellar ataxia along with hypogonadotropic hypogonadism,[39] whereas MJD is characterized by progressive cerebellar ataxia that results in loss of muscle co-ordination.[40,41] Mutations in *RNF216* and *OTUD1* genes are also associated with GHS syndrome. Patients with these mutations have similar neurological characteristics to the

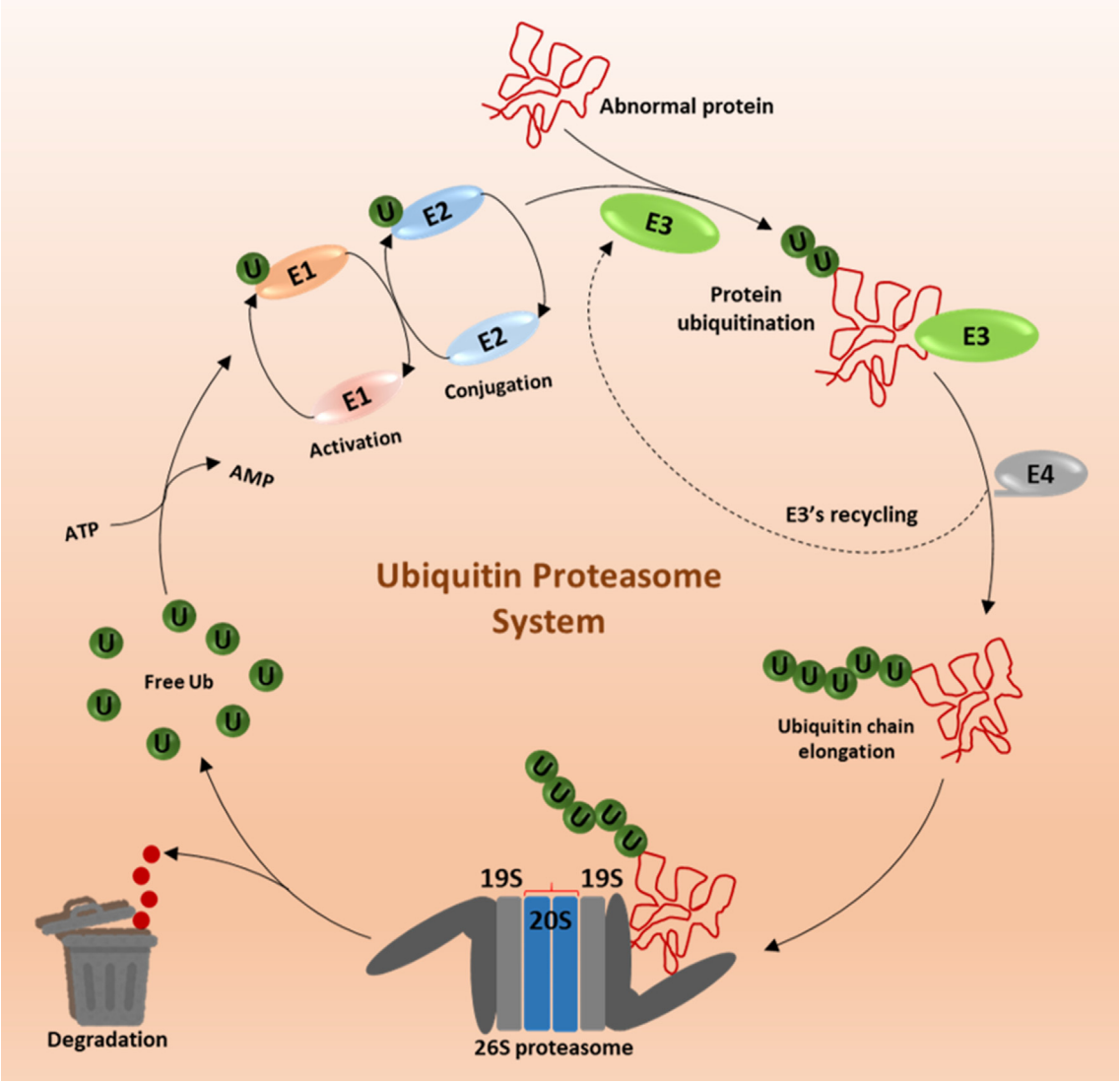

Figure 1 Ubiquitin proteasome system (UPS). ATP mediated activation of free ubiquitin molecules occurs via binding of free ubiquitin to the ubiquitin binding enzyme (E1's) through a thioester linkage, subsequently the activated ubiquitin molecule gets transferred to ubiquitin conjugating enzymes (E2's). This Ub-E2's subsequently forms a complex with abnormal protein and with a specific E3 ubiquitin ligase enzyme which is responsible for transferring the ubiquitin moiety to the amino acid residue lysine present within the abnormal client protein that leads to poly-ubiquitination and 26S proteasome mediated degradation. Extensive role of E3 ubiquitin ligases as an E4 enzyme discovered recently as a new component of UPS is responsible for the elongation of ubiquitination chain. Finally, the ubiquitin molecules are recycled and again gets involved in next cycles of UPS.

patients with *STUB1* gene mutations.[35,42] Furthermore, *STUB1* gene mutation also attenuates E3 ligase activity and results into inhibition of proteasome mediated degradation of client protein hypoxia inducible factor-1 alpha (HIF1α).[43] Till date, the limited number of studies has been performed over the *STUB1* gene mutations and its involvement in the disease prognosis. Thus, more attention and focused research is needed in the area of *STUB1* gene mutations borne diseases.

Architectural alignment

CHIP contains three TPR repeats at amino terminus, Ubox domain at its carboxyl terminus and both the structural units are integrated through a bridge called helical hairpin (HH) (Fig. 2A).[28] Three sets of anti-parallel alpha helices are present in all three TPR repeats. The structural linkage between 1st and 2nd TPR repeats or 2nd and 3rd TPR repeats look like a 'Knob and Hole' structure. Hydrophobicity of this structure plays a key role in protein—protein interaction through each TPR unit.[44,45] Association of client proteins with TPR domain of CHIP mostly occurs through molecular chaperones like HSC70/HSP70 and HSP90 [29,46,47]. Additionally, some reports revealed that TPR domain may also interact directly with client proteins in a chaperone independent manner.[48] The extended seventh helix present at the end of third set of TPR repeat is connected to helical hairpin. Two extended long alpha helices containing 'Helical Hairpin' (HH) further associates

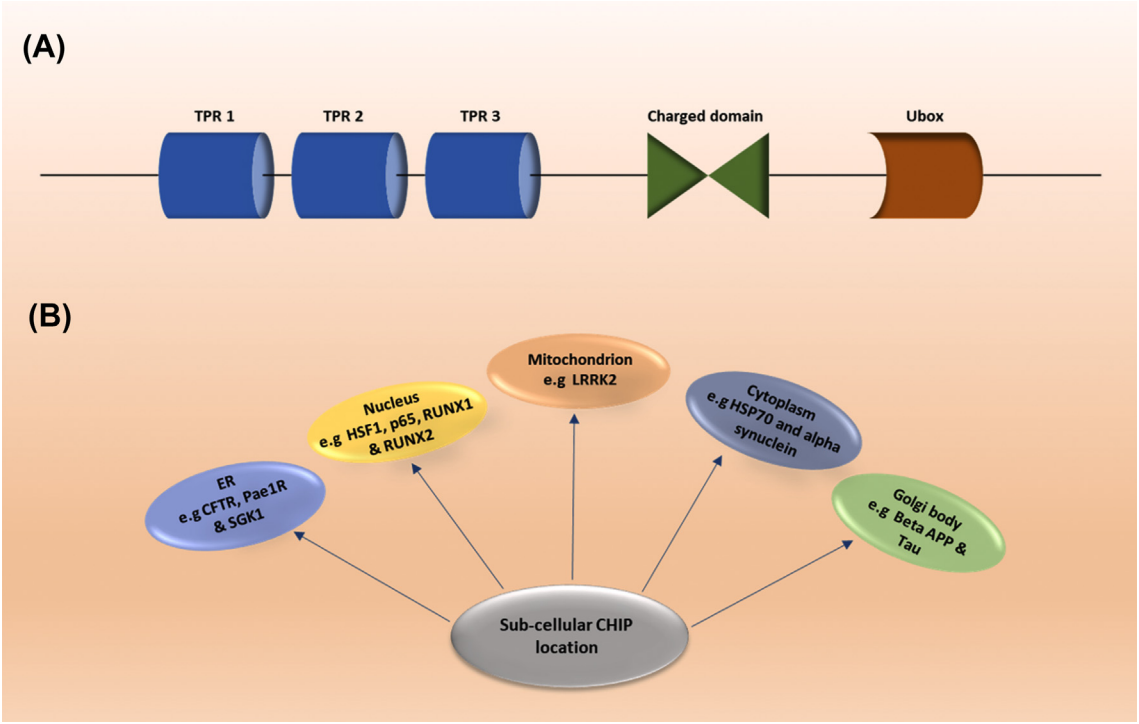

Figure 2 Architectural alignment and subcellular localization of CHIP. (**A**) The schematic diagram represents the architectural alignment of all the three domains (TPR, Ubox and Charged) of CHIP. TPR (tetratricopeptide repeats) domain is present at the N-terminus of CHIP, while Ubox domain is at C-terminus. The charged domain is localized in between TPR and Ubox domains of CHIP. (**B**) The diagram represents the sub-cellular localization of CHIP in endoplasmic reticulum (ER), mitochondria, cytoplasm, nucleus and golgi bodies.

with Ubox domain. Ubox domain is organized as "*Two beta hairpin - 1*st *alpha helix - 3*rd *beta hairpin - 2*nd *alpha helix*".[49] Previously, E3 ligases are belonged to HECT and RING finger family. Later it was established that the E3 ligases cause poly-ubiquitination and found that it belongs to Ubox family.[50,51] Ubox family is quiet similar to RING finger domain, only difference is that RING finger domain containing family is stabilized by Zn binding whereas Ubox family is stabilized by hydrogen bonding, and rest remains same.[52,53]

Tissues specific expression and subcellular localization

In general, protein CHIP is expressed in almost all type of tissues, but the expression levels differ in different tissues. Tissues having high expression of CHIP are skeletal muscle, heart, and brain whereas pancreas, lung, liver, placenta, and kidneys express CHIP at low levels. Generally, tissues with more metabolic activity and protein turnover have high CHIP expression level.[46]

At the time of discovery, CHIP was studied as a cytoplasmic protein, but as the research proceeds in last few decades various studies revealed that CHIP is widely distributed throughout the cell[28] (Fig. 2B). According to the literature CHIP is localized at various cellular regions and compartments but its expression is not fixed at any specific region or compartment of the cell. Client proteins of CHIP like CFTR,[54] Pae1R[55] and SGK1[56] co-localizes at endoplasmic reticulum (ER) for ubiquitination mediated proteasomal degradation. Furthermore, CHIP interacts with HSF1 and is localized within the nucleus.[57] Some reports also revealed that co-localization of CHIP and its association with client proteins specifically occurs in nucleus rather than cytoplasm *viz.*, p65 [58], RUNX1[59] and RUNX2.[60] Another study indicates that CHIP also maintain homeostasis of mitochondrial proteins along with cytoplasmic proteins e.g., leucine rich repeat kinase 2 (LRRK2).[61] CHIP further maintains the balance of those proteins which are present in golgi body *viz.*, β-amyloid precursor protein (β-APP)[62] and Tau.[63] Additionally, proteins such as HSP70[64] and α-synuclein[65] interact with CHIP at cytoplasm. Thus, the literature review revealed that CHIP is mostly present in cytoplasm and partly distributed in the nucleus. TPR domain of CHIP is associated with client proteins *via* chaperones (*viz.*, HSP70, HSP90, etc.) for maintenance of cellular threshold. So, in the next section we are interested to discuss the protein folding-refolding mechanism and CHIP mediated disposal mechanism of abnormal proteins.

Molecular chaperones and CHIP

Molecular chaperone (*viz.*, HSC70/HSP70 and HSP90) contains ATPase domain and carboxyl terminus domain (CTD) at its N-terminus and C-terminus respectively, plays important role in proper folding of the newly synthesized polypeptides as well as refolding of the abnormal/misfolded proteins.[66] CHIP through its N-terminus TPR domain

associates with the CTD of molecular chaperones (HSC70/HSP90). Refolding, proteasomal degradation and lysosomal degradation of abnormal or malfunctioned proteins depends on the interaction of molecular chaperones with the CHIP.[28,67] Here, we classified the mechanism of association of E3 ligase CHIP with the molecular chaperones into three types: (a) HSC70/HSP70 dependent, (b) HSP90 dependent and (c) Direct mechanisms for degradation of client proteins (Fig. 3).

HSC70/HSP70 *dependent mechanism*

HSC70/HSP70 is a molecular chaperone; with the help of co-chaperones, it promotes either the proper refolding of the abnormal/unfolded/improperly folded proteins to their native states or CHIP mediated proteasomal or lysosomal degradation.[28,67,68] HSC70 — HSP40 complex promotes protein folding while E3 ligase CHIP competes with HSC70-HSP40 complex for degradation.[69–74] Literature review suggests that chaperones *viz.*, HSC70/HSP70 and HSP90 are actively competes with each other for re-folding of abnormal client proteins to their native form.[75,76] Furthermore, in a normal physiological conditions ATP bound HSC70 is known for its low affinity for substrates and for its fast exchange rate while both the conditions are reverse for ADP bound HSC70/HSP70.[28,46,77] Co-chaperones both HSC70 interacting protein (HIP) and HSP40 binds with the N-terminus ATPase domain of HSC70. HSP40 increases the ATPase activity of N-terminus domain of HSC70/HSP70 while HIP enhances the affinity of client proteins by stabilizing the ADP-bound form of HSC70/HSP70.[46,78] 'CHIP triage' is a condition which decides chaperone bound client proteins either refolded back to its native state or degraded by proteasomal or lysosomal pathway.[67] Additionally, recent reports revealed that chaperone and proteasome system compete, where chaperone system try to save proteins by proper folding while proteasome try to dispose-off the damaged proteins. Some reviews suggest that decision is also dependent on the state of misfolded protein or amount of abnormality in the protein. Chaperone system will try to refold the abnormal proteins, if not possible then proteasomal system will dispose-off the damaged proteins.[46,75,79–82] CHIP attenuates the HIP functionality and inhibits HSP40 ATPase activity, that results in

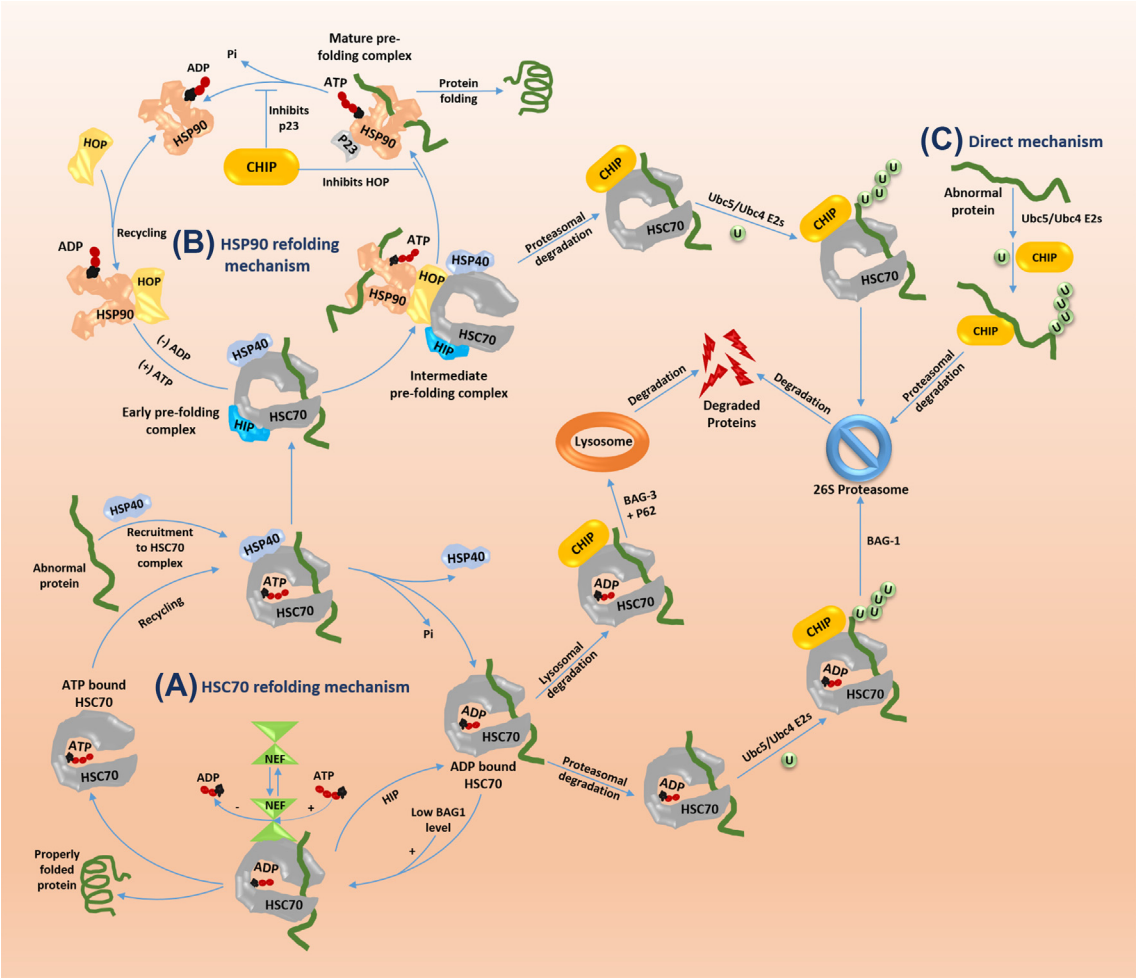

Figure 3 Molecular chaperones (HSP70/HSC70 and HSP90) dependent, independent and direct mechanisms of CHIP mediated degradation of client proteins. CHIP mediated degradation of client proteins through inhibition of either (A) HSP70/HSC70 mediated refolding; (**B**) HSP90 mediated refolding or, (**C**) Chaperones independent route for degradation of client proteins. Arrows indicate either positive (solid) or negative (T shaped) regulation.

the inhibition of HSP70 dependent refolding cycle.[28] HSC70/HSP70 bound client proteins may be degraded either through proteasomal degradation (BAG1 mediated) or lysosomal degradation (BAG3 mediated). BAG1 is a HSP70 associated co-chaperone that in a low concentration promotes the folding of proteins while in a high concentration it promotes the degradation of abnormal proteins through the 26S proteasome.[83–89] Secondly, in some cases BAG3 recruits p62 to CHIP-HSC70/HSP70 complex. Due to this switching of degradation pathway from UPS to chaperone assisted selective autophagy (CASA) occur.[85,90] Furthermore, BAG2 is a co-chaperone which inhibits the E3 ligase activity of CHIP that promotes the client protein HSP72 refolding by reducing its ubiquitination.[91,92]

HSP90 dependent mechanism

Abnormal proteins are also either refolded back into their native functional state through HSP90 mediated refolding mechanism or may get degraded with the involvement of CHIP-HSP90 complex. According to the literature review, both CHIP-HSC70/HSP70 and CHIP-HSP90 complexes competes with each other, to prove their importance in maintaining proteome health. But according to documented reports CHIP-HSC70 complex plays a crucial role in majority of the abnormal proteins poly-ubiquitination and degradation rather than CHIP-HSP90 complex. Thus, these studies concludes that 80%—90% of CHIP client proteins degradation were documented with the involvement of CHIP-HSC70 complex while 10%—20% of client proteins degradation were documented through CHIP-HSP90 complex.[93,94] In a HSP90 dependent mechanism, HSP90 associates with major co-chaperones *viz.*, p23 and HOP.[28,94–96] Co-chaperone p23 associates with ATPase like activity domain of HSP90 and responsible for reducing its ATPase like activity, that results in stabilization of the ATP bound state of HSP90.[8] Co-chaperone HSC70-HSP90 organizing protein (HOP) consists of two TPR domains 1 at N-terminus while other at its C-terminus. HSC70-HSP90 organizing protein (HOP) acts like a bridge between HSC70 and HSP90, both the chaperones work in collaboration to maintain cellular integrity of proteome. N-terminal TPR domain of HOP associates with the CTD of HSC70/HSP70 while C-terminal TPR domain of HOP associates with CTD of HSP90.[28,78] Furthermore, in HSP90 dependent mechanism 'early pre-folding complex' is formed with the association of HSC70, HSP40, HIP and client protein. Both TPR domains of HOP unites the HSP90 chaperone with the early pre-folding complex that is known as 'intermediate pre-folding complex'.[28,29] This complex also contains co-chaperones associated with the HSP90 *viz.*, p23, immunophilins etc. along with early pre-folding complex. With the utilization of ATP (through hydrolysis), dissociation of intermediate pre-folding complex occurs and transfer the client protein to HSP90-p23 complex known as 'mature pre-folding complex' or "HSP90-p23-client protein". Mature pre-folding complex refolds the abnormal polypeptides into their functional native form.[28,94,97–99] E3 ligase CHIP and p23 have their different binding sites at HSP90 but they are allosteric inhibitor to each other. Thus, the outcome of HSP90 dependent mechanism for folding/degradation is totally dependent on the competition between CHIP and p23. Furthermore, multiple reports states that if the chaperones are not able to restore unfolded/misfolded proteins back into their native form, then E3 ligase CHIP hijacks the HSP90 mediated folding mechanism by inhibiting the functionality of co-chaperones *viz.*, p23 and HOP. Finally, CHIP-HSC70 complex containing client proteins gets ubiquitinated in the presence of Ubc4/Ubc5 E2's and degraded through the 26s proteasome.[26,28,68]

Direct mechanism

E3 ligase CHIP also degrades abnormal proteins in a chaperone independent manner. CHIP by consuming its internal binding ability to ubiquitinate, degrade the abnormal proteins through E2,s (Ubc5/Ubc4) and 26s proteasome dependent route without any involvement of molecular chaperones.[48] Abnormal proteins those having slow refolding mechanism are directly ubiquitinated and disposed by E3 ligase CHIP *viz.*, smad1,[100] smad3[101] and CLEC-2.[102] Till date, there is no such evidence found related to the conditions under which cellular proteome will undergo any selected mechanisms for the degradation of client proteins. Thus, this is one of the major questions left to answer, we want to draw attention of readers to study the conditions under which CHIP is selecting the way of client protein degradation out of these three mechanisms.

Major functions of CHIP

CHIP is documented for its well-established roles in physiology as well as in various human diseases.[103] Here, we enlightened the fate of E2s - E3s interactions; crucial physiological functions of CHIP as E4 ligase and in DNA repair, maintenance of cellular protein homeostasis and metabolism.

E2s and E3s interactions — rules the fortune of client proteins

E2s and E3s are mostly responsible for deciding the fortune of a client protein along with the involvement of other components of UPS. Ubiquitin binding domain of E2 family enzymes is highly conserved. These E2s work with E3s in a collaborative manner and decides the fortune of client proteins, by addition of ubiquitin moiety to specific lysine residue.[104] Previously, E2 enzyme UbcH5 was known to be associated with E3 ligase CHIP without any lysine (K) residue specificity and it played a critical role in CHIP mediated ubiquitination, but the motifs for this interaction were not studied. Afterwards in many other reports, researchers found that ubiquitination of client proteins in the presence of UbcH5 and CHIP occurred *via* K-48 linkage.[105] Furthermore, E3 ligase CHIP is also reported to associate with dimeric Ubc13-Uev1A E2 complex, and this interaction leads to poly-ubiquitination of client proteins *via* K-63 linkage. Additionally, researchers have successfully found a common motif (Ser-Pro-Ala) responsible for interaction between E2 enzymes (*viz.*, UbcH5, UbcH4 & Ubc13-Uev1A) and Ubox domain of E3 ligase CHIP.[104] A specific case of client protein ubiquitination *via* CHIP in association with

both UbcH5 and UbcH6 E2 enzymes is also reported e.g. interferon regulatory factor 1 (IRF-1).[106] Another group have found that eight E2 enzymes (*viz.*, Ube2D1, Ube2D2, Ube2D3, Ube2E1, Ube2E2, Ube2E3, Ube2N and Ube2W) can specifically interact with Ubox domain of CHIP.[107] Thus, CHIP can interact with a number of E2 enzymes and the outcome is too much complex and different for each interaction, hence much more research is needed in this area.

Can CHIP play like an E4 ligase?

Yes, CHIP can act like an E4 ligase and due to this it enhances the length of ubiquitin chain to the client proteins along with some other components of UPS.[13] Most of the E3 ligases belongs to well-known families like HECT and RING, but in last two decades Ubox family of E3 ligases was documented as a third family represented as E4 ligases.[50,51] UFD2 is the first Ubox containing protein having E4 ligase activity in yeast.[50,108] A recent study revealed that CHIP is the first E3 ligase reported as an E4 ligase in mammalians e.g., CHIP mediates degradation of Parkin Associated Endothelin like Receptor (Pael receptor; Pael-R) along with Parkin in neurological disease Parkinson. Thus, this study clearly indicates that CHIP extends the ubiquitin length over Pael-R by acting as an E4 ligase and causes proteasomal degradation. Furthermore, E3 ligase CHIP also participates along with other E3 ligases in a mutual partnership.[55,109]

CHIP plays an important role in DNA repair

Base excision repair (BER) is a crucial pathway to restructure smaller breaks of DNA such as single-strand breaks, base damage, and base loss. X-ray repair cross complementing group-1 (XRCC1), DNA polymerase β and DNA Ligase IIIα provides a platform to produce error less transcription and replication of damaged DNA.[110–114] As reported in recent literature, CHIP plays an important role to control cellular levels of BER proteins. XRCC1 protein helps in the formation of DNA repair complex over the damaged DNA and stabilizes the BER proteins. CHIP in a chaperone independent manner ubiquitinates and degrades the excess BER proteins that are not taking part in DNA repair complex.[115] Still the mechanism by which CHIP differentiates between excess and chromatin associated BER proteins is not documented yet. Thus, these findings suggests that CHIP plays a significant role in DNA repair system.

CHIP maintains the cell/tissue homeostasis

CHIP plays a crucial role in the maintenance of cellular homeostasis in normal as well as under various stress conditions. In the heat stress condition, apart from ubiquitination of mis-folded proteins, CHIP has been reported to interact and selectively degrade the misfolded/denatured proteins in a HSP70 independent manner. Surprisingly, CHIP stabilizes the HSP70-protein complexes to number folds in the presence of CHIP rather than its absence. Molecular mechanism underlying the contradicting dual role of CHIP in normal *vs* stress conditions is not fully understood yet.[48] Additionally, CHIP also plays a protective role for maintaining the proteome health in induced oxidative stress conditions. Recently, it has been found that CHIP degrades the endonuclease G in normal condition but not in H_2O_2 induced oxidative stress. Still the question is remains to be answered that how CHIP is differentiating the endonuclease G in normal and oxidative stress conditions.[116] However, in response to osmotic stress, it has been reported that activation of p38MAPK, JNK and ERKs occurs in mammalian cells.[117] In sorbitol induced osmotic stress, MEKK is dephosphorylated and results in CHIP mediated ubiquitination and degradation.[118] Thus, these findings suggests that CHIP plays a protective role in maintaining homeostasis against heat stress, oxidative stress, and osmotic stress. Furthermore, CHIP maintains cellular homeostasis in various stress conditions by regulating various stress induced disease factors classified as: enzymes (*viz.*, ChAT,[119] DLK,[120] proto-Db,[121] Endo G,[122] Hsp70,[123,124] Hsp72,[92] Hsp90,[124,125] NOX4,[126] SENP3,[127] SirT6,[128] SGK1,[56] SGK3[129] and SOD2[130]); signaling intermediates (*viz.*, AIF,[131–133] ASK1,[134,135] ERK1,[136] IRF-1 [137–139] and MEKK2[118]); transcriptional factors (*viz.*, GR[67,140] and HIF-1 alpha[43,141–144]); receptor proteins (*viz.*, DAF-2/INSR[145]) and cytoskeleton protein Niemann-Pick C1[146]).

Additionally, CHIP also has its major role in maintaining the protein homeostasis and metabolism by regulating its various client proteins such as cytoskeleton proteins (*viz.*, aquaporin-2 [147–149], BER proteins,[115,150] PrP^C [151] and RHBDF2[152]); transcriptional factors (*viz.*, β-catenin,[153] eIF4E,[154,155] hPXR T408D mutant,[156] TEAD4[157] and AhR[125]); receptor proteins (*viz.*, GHR,[158] nicotinic receptor,[159] PPARγ[160] and BMAL-1[161]); signaling intermediates (*viz.*, MAPK3[153] and phosphatase PPP3CA[153]); and enzymes (*viz.*, AMPK proteins,[162,163] CDK4,[153] caspase 6,[164] ClpP4,[165] cytochrome P450A,[166–168] cytochrome P450 3A4,[169] NQO1,[170] NIK[171] and PRMT1[153]). Altogether, these documents conclude that CHIP maintains cellular protein metabolism and homeostasis in normal conditions as well as under stress situation.

CHIP in major human diseases

As discussed earlier, CHIP has several well established various physiological roles. In the recent past, research was focused mainly on its involvement in the initiation and progression of various human diseases such as immune disorders, neurological disorders, aging, inflammatory disorders, bone remodeling and cardiovascular disorders.

Immune system

CHIP is expressed in various immune cells such as macrophages, dendritic cells, natural killer (NK) cells, T cells, B cells etc. But still its exact role has not been studied yet in these immune cells.[172,173] CHIP has its role in regulation of nuclear factor kappa-light-chain-enhancer of activated B cells.[174,175] Previously, it was known that CHIP interacts with NF-kB-inducing kinase (NIK) through HSP70 and gets ubiquitinated and degraded. As the era proceeds, another group has also found that formation of the HSP70/NIK/CHIP dimer/TRAF3 complex increases the ubiquitination and

degradation of NIK. They also found that degradation of NIK is not dependent on E3 ligase activity of CHIP. Thus, these studies suggests that CHIP forms a complex with other proteins including target proteins and degrades these clients without its E3 ligase activity.[171,176,177] Toll like receptors play its crucial role in sensation and recognition of conserved structures of pathogens.[178,179] It has been found that CHIP interacts with TLR4/9 and TLR2/7 complexes *via* HSP70 but does not interact with TLR3.[180] CHIP binds with HSP70/protein kinase C (PKC)-ζ/SRC in TLR4/9 signaling pathway, resulting in K-63 dependent ubiquitination of both SRC and PKC-ζ, which leads to the activation of NF-κB signaling.[180] Hence, these reports suggest that CHIP degrades TLR proteins and could affect the NF-κB signaling pathway.

CHIP is also known to activate the protein kinases (*viz.*, Src/PKCζ,[180] CARMA1[181] and RIPK3[182]). K-63 linked ubiquitin chain and HSP70 are involved in the CHIP mediated recruitment and activation of Src/PKCζ protein kinase,[180] while CHIP interacts with CARMA1 protein kinase through K-27 linked ubiquitin chain and promotes NF-kB activation.[181] Additionally, CHIP mediates the RIPK3 ubiquitination and degradation through lysosomal pathway.[182] Further, CHIP regulates various nitric oxide synthases such as iNOS,[183,184] nNOS[185] and eNOS.[186] It interacts with iNOS and nNOS through both HSP70 and HSP90 chaperones dependent manner[186] and promotes K-48 linked ubiquitination and proteasomal degradation,[183–185] while eNOS interacts through HSP90 dependent manner and degraded by UPS.[186] It also plays an essential role in the proteasome mediated ubiquitination and degradation of signaling intermediate FADD.[187] Furthermore, it is found that CHIP mediates the regulation of various transcriptional factors (*viz.*, HIF-1α,[43,143,144] Foxp3,[188–190] RFX-1,[191] STAT4[192] and Tat[193]) that are involved in immune system. It interacts with both Foxp3 and RFX-1 through K-48 linked ubiquitin chain in HSP70 dependent manner and leads to its degradation by UPS,[188–191] while transcriptional factor HIF-1α interacts *via* both K-48 and K-63 linked ubiquitin chain in HSP70 dependent manner and was found to be degraded through autophagy as well as UPS.[43,143,144] CHIP also inhibits the HIV virus replication by proteasome mediated degradation of its viral component Tat.[193] Thus, all these reports conclude that CHIP may play a significant role in the regulation of various immunological factors, transcriptional factors, protein kinases and various nitric oxide synthases in the immune system.

The body's defense system can acknowledge and govern the tumorigenic cells primarily through the production of cancer specific cytotoxic T lymphocytes.[194,195] In a purpose to initiate anti-tumorigenic immune responses, various antigen presenting cells recognize and present the tumorigenic antigen to T cells. The activated cytotoxic T cells eliminate the tumorigenic cells and try to control the immune-suppressive tumor microenvironment.[195–197] The tumor microenvironment is too much complex, mostly consisting of immune cells (*viz.*, dendritic cells, neutrophils, T-reg cells, lymphocytes, monocytes and macrophages), adipose cells, fibroblasts, extracellular matrix and epithelial cells.[198,199] Additionally, overwhelming of immune surveillance and extermination are hallmark of cancers.[200,201] In the tumor microenvironment, these cells are functionally altered due to their interactions with each other, but the myeloid cells are plastic in nature in this context.[198,202] Myeloid derived suppressor cells (MDSCs), neutrophils and tumor associated macrophages (TAMs) are the primary tumor associated myeloid cells and capable to suppress the immune system. The clear distinction between MDSCs and neutrophils in tumor is not well studied yet.[203,204] However, monocytic-MDSCs are quite similar to TAMs, while polymorphonuclear-MDSCs are similar to tumor associated neutrophils.[203] Furthermore, the release of granulocytic (G-CSF), macrophagic (M-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) by tumor cells results in granulo-monocytopoiesis and extension of MDSCs in tumor microenvironment.[205] The expansion of MDSCs in tumor microenvironment is also possible in a response to pro-inflammatory cytokines IFN-γ and IL-6.[206,207] Additionally, various other cytokines (*viz.*, IL-13 and IL-4) and TGF-β are also present in tumor microenvironment and promote the immunosuppressive role of MDSCs.[208] On the other hand, TAMs are involved in immune linked cancer development as well as in tumor suppression. Presence of M1 pro-inflammatory phenotype of macrophages in tumor microenvironment encourages the tumorigenic transformation at the site of chronic inflammation, while the presence of M2 phenotype of macrophages promotes the immunosuppressive role.[209–212] Additionally, in most of the solid tumors, infiltration of macrophages is noticed[199,209,212–215] and responsible for poor prognosis *in* breast cancer, glioblastoma and lung cancer.[216–220] Thus, this review concludes that immune system tightly resembles the cancer development and tumor microenvironment. However, the role of CHIP in immunity has been well explained in the previous section. CHIP is present in various immune cells of tumor microenvironment (*viz.*, macrophages, T-cells, neutrophils, NK cells etc.), but its exact role in these cells is not studied yet.[172,173] Also, the direct role of CHIP in immune response mediated tumor development and in tumor microenvironment is not studied well. CHIP mediates the indirect regulation of inflammatory mediators, tumorigenic signaling molecules and microenvironment factors, suggesting that CHIP might has its role in immune response mediated tumor biology. As discussed earlier, CHIP mediates the regulation of TLR proteins in immune cells and results in the activation of NF-κB signaling pathway in inflammation and tumor biology. This report does not mention the impact of NF-κB signaling activation in tumor development and tumor microenvironment. But the activation of NF-κB signaling suggests that CHIP might has its impact on the correlation between immune response and tumor development.[171,176–178,180] Recently a research group has studied the Parkin mediated regulation of CHIP-IRF1 axis which controls the anti-tumorigenic immune response and found that removal of mitochondrial membrane protein Fam73b leads to the activation of IL-12 and causes the switching of mitochondrial morphology from fusion to fission. The mitochondrial dynamics is found to affect the parkin gene expression and its mitochondrial recruitment. E3 ligase Parkin inhibits the CHIP-IRF1axis and suggests the anti-tumorigenic immune response.[138] Thus, all these reports suggests that CHIP has some indirect and unknown role in immune response mediated tumor development and tumor microenvironment. We

would like to draw the kind attention of researchers to study the impact of CHIP upon the correlation between immune responses and tumor biology.

Aggresome formation and maturation

Cellular toxicity due to mis-folded proteins is operated by three different mechanisms. Firstly, mis-folded proteins try to get re-folded back to their nascent form with the help of chaperones. Secondly, if not possible to refold back, then it leads to its lysosome or proteasome mediated degradation. In the last mechanism, sequestration of mis-folded proteins/polypeptides occurs into juxtanuclear detergent-insoluble inclusion bodies called aggresome.[221–223] Recently, it was found that CHIP plays another vital role in the aggresome formation and maturation in the context to iNOS and CFTRΔF508. Lacking of CHIP increases the formation of cellular protein aggregates and inhibits aggresome maturation.[54,224] Thus, CHIP may play distinct role in aggresome formation and maturation.

Neurodegeneration

Neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis, and Huntington's disease occurs due to accumulation of non-functional, toxic and misfolded protein aggregates.[225] In the removal of these mis-folded protein aggregates of neurodegenerative diseases various E3 ligases and proteasomes are involved.[226,227] One of the E3 ligase CHIP plays an important role to maintain neural homeostasis with the involvement of HSP70, HSC70 and HSP90.[62,225,228] It has been reported that CHIP plays an essential role in the ubiquitination of various important factors of these neurodegenerative diseases such as Tau and APP in AD,[62,227,228] Ataxin-1 & Ataxin-3 in type-1 & type-3 spino-cerebellar ataxia[229,230] and malin in Lafora disease.[231,232] Mechanism of CHIP mediated protection of neural system from toxicity caused by misfolded protein aggregates is not yet fully understood. However, it has been reported that limited expression of CHIP causes neural toxicity due to protein aggregation, accumulation, and induction of stress.[226] E3 ligase CHIP plays an important role to maintain neural homeostasis with the involvement of HSP70, HSC70 and HSP90. CHIP also has roles in various neurodegenerative diseases by ubiquitination and degradation of receptor proteins (AR)[233–237]; signaling intermediates (*viz.*, Ataxin-1,[229,238] LRRK2,[61,239,240] MKKS,[241] SCAR16[227] and PINK1[242]); cytoskeleton proteins (*viz.*, α-synuclein,[65,228,243,244] FMR1,[245] mHtt,[246] Tau/Phosphorylated Tau[225,231,247–252] and PolyQ[229,253]); and various neuronal enzymes (*viz.*, BACE1,[254] Malin,[232] nNOS,[183–185,255,256] SOD1[123,257–259] and HDAC6[248]). CHIP mediated protection of neural system from toxicity caused by misfolded protein aggregates is not yet completely understood. However, it has been reported that limited expression of CHIP causes neural toxicity due to protein aggregation and accumulation as well as induction of stress.[62] Thus, multiple studies suggest that CHIP plays an essential role to maintain tissue homeostasis in nervous system.

Inflammation, bone remodeling and skin diseases

CHIP contributes in controlling inflammation through regulation of interleukins 4α receptor (IL-4Rα),[260] TNFα[261] and NF-κB.[262,263] Both interleukins- 3 and 4 signaling pathways are regulated through a common IL-4Rα receptor. CHIP interacts with IL-4Rα and leads to its UPS dependent degradation that suggests CHIP regulates the inflammation by the degradation of IL-4Rα.[264,265] In arthritis patients and inflammatory diseases, TNFα level is high which leads to the degeneration of bones and cartilages. Osterix is a novel zinc finger-containing transcription factor that is essential for osteoblast differentiation and bone formation. A recent study suggests that upon CHIP up-regulation, TNFα inhibits osteoblast differentiation due to degradation of osterix.[261] CHIP has its magnificent role in bone remodeling by degradation of various signaling molecules such as multiple SMAD proteins,[266,267] RUNX2[128,268] and TRAF family members *viz*. TRAF2, TRAF5, TRAF6.[263,269–271] CHIP mediates the degradation of multiple SMAD proteins and thus regulates TGFβ pathway and bone morphogenetic protein (BMP) signaling.[266,267] Induction of RUNX2 degradation occurs by CHIP that results in inhibition of osteoblast differentiation. NF-κB signaling has its well-known role in regulation of bone remodeling.[128,268] CHIP degrades various TRAF family proteins and leads to inhibition of NF-κB signaling. Authors also found that nuclear translocation of NF-κB subunit p65 is increased upon *STUB1* gene knock out in mice, resulting in reduction of osteoblast formation.[263,269–271] Thus, these findings suggest that CHIP may play a significant role in inflammation and bone remodeling. On the other hand, CHIP plays a tremendous role in skin diseases by regulating cytoskeleton protein (keratins[272]) and enzyme (NUCB1[273]). Thus, all these findings indicate that CHIP may play significant roles in inflammation, bone remodeling and skin diseases.

Aging and development

Aging is a phenomenon which is characterized by structural and functional changes in all tissues and organs, resulting in reduction of regenerative capacity of tissues. In the later stage of aging, increment in production and accumulation of toxic protein aggregates occurs due to reduction in chaperones and proteasomal activity.[228,274] Recent studies reveal that HSP70 has a direct link with aging.[275,276] CHIP plays its beneficiary role in cellular hemostasis as well as in the control of aging process. It has been reported that in *STUB1* deficient mice, lagging related biomarkers are increased due to accumulation of toxic proteins.[277] Expression of leucine rich repeat kinase-2 (LRRK2) is high in *STUB1* KO mouse model of PD. Level of LRRK2 is down-regulated due to increased expression and activation of cellular CHIP.[225,240] Additionally, CHIP controls aging induced hyper-activated biomarkers such as Sirtuin 6 (SIRT6)[278,279] and insulin receptor.[145,280] Thus, these findings concludes that CHIP plays an essential role in controlling the aging process. Further, CHIP regulates various developmental processes by regulating signaling intermediates (Ca^{2+}/S100);[281] transcriptional factors (myocardin[282] and RUNX2[60]); various enzymes (*viz.*, NEK10,[283]

PABPN1,[284] ribosomal Protein S3,[285] TFEB[286] and IRE1[287]); and cytoskeleton proteins (*viz.*, KCNQ4,[288] katanin-p60[289] and plastid precursors[290]). All together these findings conclude that CHIP plays a necessary role in aging and developmental processes in the human body.

Aging is highly correlated with cancer where aging is considered as a pro-tumorigenic state.[291,292] Number of cellular processes such as accumulation of senescent cells in tissue results into tissue degeneration. Changes in genes and chromatin structure, stem cell impairment and autophagy are probable factors responsible for aging mediated pro-tumorigenic environment.[293–299] However, chaperone associated E3 ligase CHIP has its extensive role as an anti-aging agent as discussed in earlier section. But none of these reports has clearly discussed the role of CHIP on aging mediated tumor development and in tumor microenvironment, and hence requires immediate attention.

Cardiovascular diseases

CHIP is highly expressed in heart tissues and behaves like a cardio-protective agent in heart diseases.[28] Recently in a couple of reports CHIP has been linked with cardiac crashes. Accumulation of p53 in cardiac myocytes is the major feature of ischemic heart diseases.[298] This report suggests that CHIP is an important E3 ligase responsible for p53[299,300] and HIF-1α[300] degradation. In the coronary occlusion condition, hypoxia is generated in cardiac myocytes that leads to the up-regulation of HIF-1α and down-regulation of CHIP expression and eventually the ischemic heart diseases.[300] Overexpression of CHIP in combination with HSP90 inhibition (using 17AAG) leads to the cardio-protective effects.[299] Further, in various reports CHIP has been studied as a beneficiary factor in cardiac diseases by degrading its client proteins classified as transcription factors (*viz.*, ICER[301] and NFATc3[302]); cytoskeleton proteins (*viz.*, HERG,[303] Kv1.5[304] and NaCl co-transporter[305]); and signaling intermediates (*viz.*, Gαs[306] and SHP-1[307]). Thus. CHIP is an eminent cardio-protective agent.

Currently, variety of chemotherapeutic agents has been developed and are used in clinical practice for cancer therapy *viz.*, antimetabolites, platinum-based agents, alkylating agents, anti-microtubular agents, anthracyclines and antitumor antibiotics. Additionally, various targeting agents (*viz.*, immune checkpoint inhibitors, small molecule inhibitors and HER2 inhibitors) are also developed for cancer therapy. However, the cardiotoxicity is noticed as a prominent side effect of these chemotherapeutics. Cardiotoxicity induced by chemotherapeutics may include cardiac cell damage, abnormalities in cardiac impulse conduction, reduction in left ventricle ejection rate and fraction, disturbance in blood pressure etc.[308–313] Sunitinib malate is a small molecule tyrosine kinase inhibitor having anti-tumorigenic activity against gastrointestinal, pancreatic, neuroendocrine tumors and advanced renal cell carcinoma. The use of sunitinib is noticed to produce cardiotoxic side effects such as vascular disturbances in thromboembolic events, hypertension, heart failure and occasionally may leads to death. In the management of these side effects, various other pharmacological agents are currently used. For thromboembolic events, low molecular weight heparins (LMWH), rivaroxaban and edoxaban are preferred; to manage hypertension, angiotensin inhibitors and calcium channel blockers are preferred; and in the management of heart failure clinicians are preferring angiotensin inhibitors and cardio-selective beta blockers.[308] Recently, a research group has demonstrated the use of geldanamycin (HSP90 inhibitor) to attenuate the sunitinib induced cardiotoxicity and found significant reduction in sunitinib induced cytotoxicity in rat H9C2 cardiomyocytes. They also tried with the use of other HSP90 inhibitors such as tanespimycin, BIIB021 and ganetespib in sunitinib induced heart toxicity model. Sunitinib originated cardiotoxicity is due to the induction of autophagy in H9C2 cells, while in combination with geldanamycin sunitinib induced autophagy was inhibited and induced the degradation of various autophagy associated proteins *viz.*, Atg7, ULK1 and Beclin-1. It also demonstrated the inhibitory effects of geldanamycin in sunitinib induced cardiotoxicity in pluripotent stem cell derived cardiomyocytes. Hence, these results conclude that HSP90 inhibitors in combination with sunitinib may be a potential strategy to attenuate the cardiotoxicity of sunitinib.[314] Furthermore, doxorubicin (DOX, an anthracycline based antibiotic) is also preferred in chemotherapy against prostate, cervix, breast, brain cancers and in Hodgkin's lymphoma. Lower ventricle failure, arrhythmia and heart failure are primarily noticed cardio-toxic side effects in DOX treatment. Often clinicians prefer antiarrhythmic agents to manage DOX-induced arrhythmia, while beta blocker (carvedilol) and ACE inhibitor (enalapril) are much preferred to manage doxorubicin induced heart failure and ventricular dysfunction.[308] Recently, a research group has studied the inhibitory action of 17-AAG in DOX-induced cardiotoxicity.[315] And another group has demonstrated that doxorubicin induced cardiotoxicity may be attenuated upon the treatment of cardiomyocytes with 17-DMAG.[316,317] Thus, these studies suggest that DOX-induced cardiotoxicity may be nullified, if the HSP90 inhibitors were used in combination. At present, HSP90 inhibitors in combination with DOX and sunitinib is only studied to prevent their cardiotoxicity.[314,315,317] Thus, researchers and clinicians should explore more on this strategy with an objective to control cardiotoxicity of cancer chemotherapeutics.

We have enlightened above the responsibility of CHIP in normal physiology as well as in several diseases such neurodegenerative disorders, immunological disorders, cardiac disorders, aging, inflammatory disorders, bone remodeling and skin diseases to maintain the protein quality and control the cellular threshold of clients. But in the recent era of CHIP, it is studied for its fundamental role as a double agent in cancer and most of the substrates reported till date are involved in cancer initiation and progression. Mostly, CHIP is documented for its tumor suppressor role over its oncogenic actions. Further, we are interested to focus on clinical significance of CHIP in various cancers and its involvement as a double agent.

CHIP: a double agent in cancer

In the year of 1998, CHIP was screened and discovered in heart tissue by Ballinger and his group. It plays a critical role through maintenance of protein quality and control the cellular threshold of client proteins.[28,67] Its role is totally un-predictable but depends upon the status of target proteins.[28,67] After its discovery, several substrates of CHIP were documented, and its involvement was found in several human diseases as discussed in the earlier sections of this review. Here authors retrieved almost all the documented substrates till December 2020 and have represented all of them in a pictorial timeline, according to the year of discovery (Fig. 4).

CHIP has its wide variety of functions in normal physiology as well as in several diseases including cancer.[27] Also, the documented client proteins were also classified in context of various disease perspectives (Table S1). Surprisingly, it is found that in the last decade, most of its substrates were documented to be involved in cancer. It was found to have a double role (either as a tumor suppressor or as an oncogene) in many cancers. Hence, we classified the substrates further according to the hallmarks of cancer[200,318,319] in the context of its role as an oncogene and a tumor suppressor[144,172,320] (see Fig. 5). Here, we have tried to focus on both the opposing roles of CHIP in cancerous scenario.

Acts as a tumor suppressor

In a pioneer study CHIP has been found as a key mediator that regulates the breast cancer progression. They found that CHIP level is negatively correlated with tumor growth and metastasis in a breast cancer model of nude mice.[321] In support of this pioneer study, series of reports have been published showing the active involvement of CHIP in different cancers; this certainly creates an important debate. These reports suggest that CHIP may play as a tumor suppressor *via* interacting and proteasomal mediated degradation of onco-proteins. Here, in this study we made a survey of reported substrates of CHIP in cancer till date and classified them under various hallmarks of cancer (Fig. 5). In few reports, it has been observed that CHIP may acts as a tumor suppressor with the inhibition of inflammatory hallmark of cancer. In the aspect of tumor suppressive action of CHIP, it interacts with few inflammatory mediators, leading to ubiquitination and proteasome dependent degradation of target proteins *viz.*, MIF,[322] MAST1,[323] CD166,[324] FGFR3[325] and ISG15.[326] Often, MIF-HSP90 chaperone complex is reported as a highly stabilized complex in various human cancers and responsible for tumor aggressiveness. Inhibition of HSP90 chaperone with 17AAG or HSP90 specific siRNA, promotes the E3 ligase CHIP mediated MIF degradation and leads to the inhibition of inflammatory characteristics in breast cancer model.[322] CHIP mediated regulation of FGFR3 also occurs through the same mechanism. Additionally, microtubule-associated serine/threonine kinase 1 (MAST1) is studied as a responsible factor for cisplatin resistance in multiple human cancers. Recently, through proteomic analysis a research group has shown HSP90B chaperone as an interacting partner and stabilizing factor of MAST1. Further, they have found E3 ligase CHIP mediates the degradation of MAST1, upon the inhibition of HSP90B chaperone and results in the improvement of cisplatin effectiveness. Thus, this report suggests that HSP90 inhibitors in combination with cisplatin may be an effective strategy to overcome the cisplatin resistance.[323] Recently, a research group studied CD166 in head and neck (H&N) cancer to investigate the CHIP linked molecular mechanism and found that CHIP mediates the degradation of CD166 and leads to the inhibition of inflammatory characteristics of H&N cancer.[324] Thus, all these mechanistic reports clearly indicate that how CHIP may govern the inflammatory hallmark of tumor biology.

Similarly, CHIP is negatively correlated with various substrates *viz.*, AXL,[327] C-ErbB2/Neu,[173,320,328–331] BCR-ABL,[332,333] EGFR,[334–336] EZH2,[337] PKM2,[338] p42 Ebp1,[339] PRMT5,[340] OCT4[341] and trans-glutaminase 2[342]; results in the inhibition of tumor progression. Tyrosine kinase AXL receptor is highly expressed in multiple cancers and primarily responsible tumor progression. 17AAG dependent

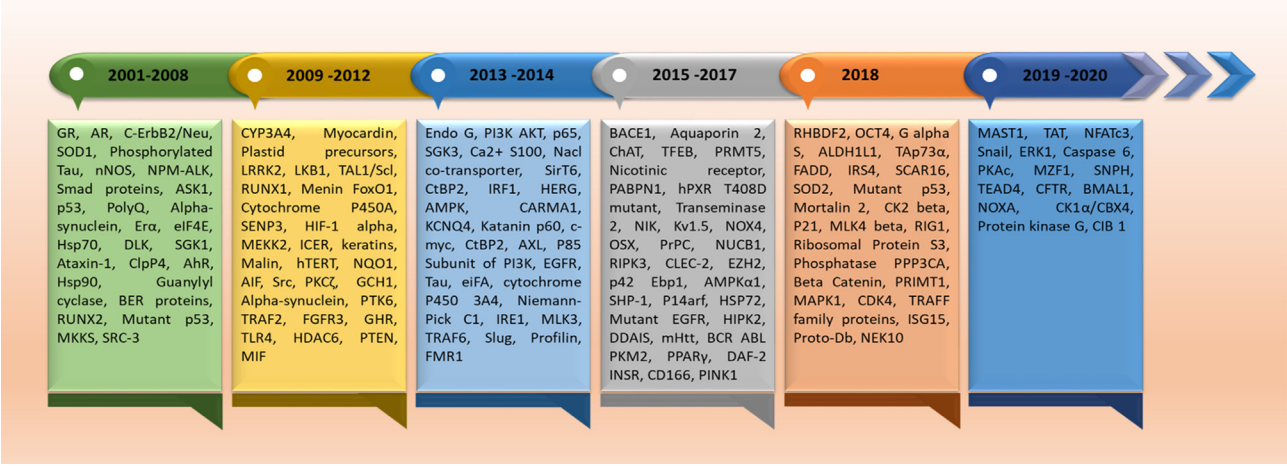

Figure 4 Timeline for client proteins of CHIP. The figure depict the timeline of all documented client proteins of CHIP identified till December 2020.

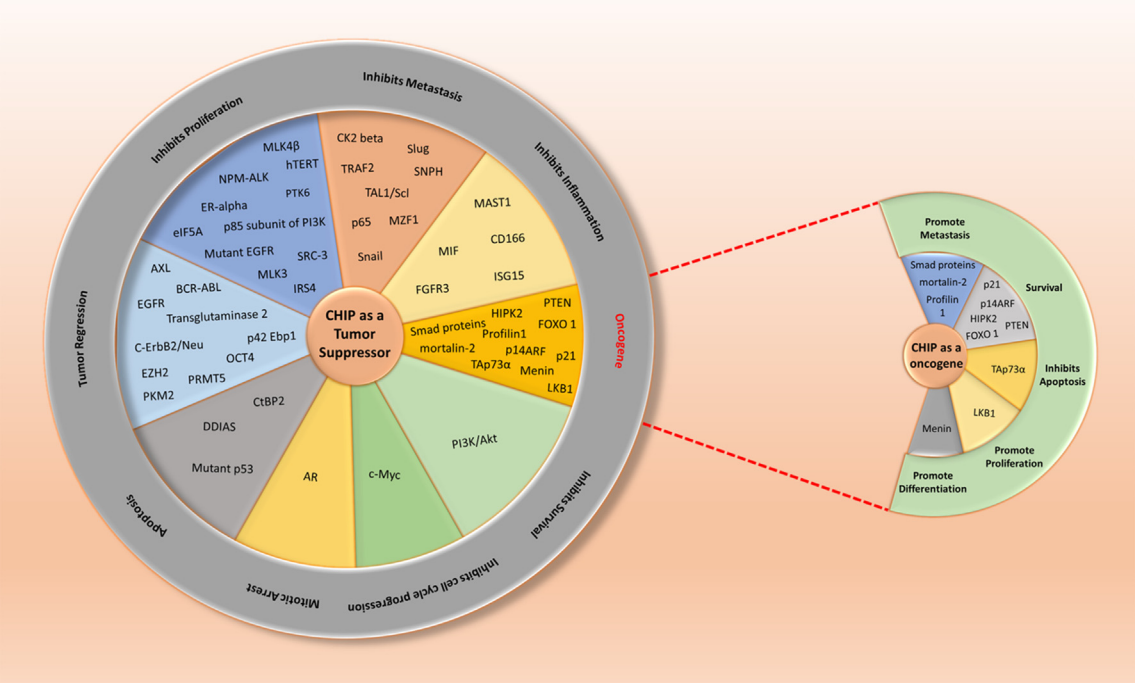

Figure 5 Pie-in-pie chart of CHIP as a double agent in the context to cancer. CHIP client proteins classified according to the hallmarks of cancer and its dual role as a tumor suppressor (left hand sided pie chart) and as an oncogene (right hand sided pie chart) explained.

inhibition of HSP90 chaperone leads to destabilization of AXL through CHIP mediated degradation, resulting in inhibition of tumor progression.[327] Furthermore, tyrosine kinase inhibitor imatinib is a primary drug in myeloid leukemia but resistant in chronic myeloid leukemia patients due to high expression of BCR-ABL protein. Chk1 inhibitors (AZD7762 and MK-8776) as well as oridonin promote CHIP mediated degradation of BCR-ABL protein in chronic myeloid leukemia cells. Thus, targeting Chk1 or treatment with oridonin may help to overcome the imatinib resistance in chronic myeloid leukemia patients.[332,333] CHIP acts as a tumor suppressor through degradation of EGFR and its mutated forms those highly expressed in cancer.[334–336] Next, CHIP can degrades oncogenic protein enhancer of zeste homolog 2 (EZH2) A novel EZH2 targeting molecule (derivative of gambogenic acid) is recently identified which covalently binds EZH2 at cys668 and promotes CHIP mediated degradation.[337] Recently, through SILAC based proteomics study a research group has found pyruvate kinase isoenzyme M2 (PKM2), an important regulatory factor for aerobic glycolysis (Warburg effect) and tumorigenesis, is a novel target protein of E3 ligase CHIP and maintain an inverse correlation in ovarian carcinoma. Thus, the Warburg effect is regulated through CHIP mediated degradation of PKM2.[338] Furthermore, CHIP is expressed at low level in cancer stem cells that regulates the OCT4 stability through direct interaction and maintain an inverse correlation in breast cancer.[341] Taken together, these mechanistic reports suggest that CHIP acts as a tumor suppressor that controls tumor regression hallmark in cancer.

It has been also found that CHIP inhibits cellular proliferation by ubiquitination and degradation of various substrates *viz* MLK4β,[343] NPM-ALK,[344] PTK6,[345] ER-alpha,[346–351] mutant EGFR,[334] eIF5A,[352] hTERT,[331] IRS4,[353] MLK3,[354] p85 subunit of PI3K[355] and SRC-3.[356,357] MLK3 and MLK4β are components of MAP kinase signaling pathway which regulates cellular responses like proliferation, invasion, and apoptosis. Expressions of MLK3 and MLK4β are inversely correlated with osmotic stress/thermo stress/HSP90 inhibition due to CHIP mediated degradation which results in decreased cellular proliferation of ovarian cancer cells.[343,354] Similarly, inhibition of HSP90 chaperone with 17AAG promotes degradation of anaplastic lymphoma kinase (ALK)[344] and PTK6,[345] suggesting tumor suppressive action of CHIP.

In the screening of its substrates, it was also found that CHIP inhibits metastasis of tumor cells by targeting CK2β,[358] slug,[359] SNPH,[360] TRAF2,[361,362] TAL1/Scl,[321] MZF1,[363] p65 [364] and snail.[365] Activation of protein kinase CK2 promotes the TGFβ mediated epithelial mesenchymal transition. CHIP mediates the degradation of CK2β and results in inhibition of invasion and migration in tumor cells.[358] Additionally, GSK3β mediates the slug phosphorylation that leads to its degradation by CHIP and prevent metastasis in lung cancer.[359] CHIP negatively regulates the NF-κB signaling by downregulating TRAF2.[362,363] A recent report indicated that CHIP and snail both are inversely correlated in ovarian carcinoma. CHIP inhibits EMT through downregulation of snail, a characteristic marker protein of EMT.[365] Thus, CHIP acts as a tumor suppressor by inhibiting metastatic hallmark of cancer.

Additionally, CHIP promotes the apoptosis of tumor cells by ubiquitination and degradation of target proteins CtBP2,[116] DDIAS[366] and mutant p53.[367] C-terminal binding protein 2 (CtBP2) and DNA damage induced apoptosis suppressor (DDIAS) are involved in cellular apoptosis, migration

and tumorigenesis. These proteins are highly expressed in many cancers with low expression of CHIP. It was reported that overexpression of CHIP downregulates the CtBP2 and DDIAS proteins.[116,366] CHIP mediated ubiquitination and degradation of Androgen Receptor (AR)[368–372] results in mitotic arrest of prostate tumor cells. CHIP targets PI3K/Akt[373] and inhibits the survival power of tumor cells. Oncoprotein c-Myc plays its crucial role in oncogenesis. Our research group identified that CHIP targets and degrades c-Myc and results in the inhibition of cell cycle progression.[374] Altogether, many reports clearly indicate that CHIP can act as a tumor suppressor in multiple cancer scenarios. CHIP mRNA and protein levels are differentially maintained in normal and breast cancer tissues. CHIP level is negatively correlated with the increment of breast cancer malignancy and overall survival of high CHIP expressing tumor bearing patients is much higher than the low CHIP expressing tumor bearing patients.[375] Further, both mRNA and protein expression levels of CHIP are negatively correlated with its usual level in normal gastric tissues.[58] Thus, all these reports suggest that CHIP can act as a tumor suppressor.

Acts as an oncogene

In adverse to above mentioned reports, CHIP is also seen to act like an oncogene in few of other reports. CHIP promotes proliferation and survival of tumor cells after the degradation of its substrates *viz.*, PTEN,[172,376] FOXO1,[377] HIPK2,[378] p14ARF[379] and p21[380] which are mainly engage in tumor suppression and apoptosis. Transcriptional factor FOXO1 is responsible to control the cellular proliferation and survival. Its cellular level and activity are controlled by UPS and PI3K/Akt. Overexpression of CHIP with TNF alpha treatment downregulates the FOXO1 and promotes the PI3K/Akt pathway mediated cellular proliferation and survival. Conversely, upon its knockdown, FOXO1 gets stabilized and results in the inhibition cellular proliferation and survival.[377] Serine/threonine kinase HIPK2 plays crucial roles in DNA damage response and development. PARP1 regulates the HIPK2 protein stability. Furthermore, CHIP promotes the HIPK2 degradation in a PARP1 independent manner and suggests its oncogenic role.[378] HSP90 in combination with CHIP promotes the lysosomal pathway mediated degradation of p14ARF. While the knockdown of CHIP in combination with HSP90 inhibition gives converse results in non-small cell lung cancer.[379] Knockdown of CHIP inhibits degradation of p21 which targets the various stress related proteins and ultimately enhances the sensitivity of lung cancer cells towards radiotherapy. CHIP-HSP70-p21 axis may be potential target to improve the efficacy of radiotherapy.[380]

Similarly, CHIP is also reported to promote metastasis after the ubiquitination and degradation of SMAD proteins,[100,267,381] Profilin1[382] and Mortalin-2.[383] A research group using surface plasmon resonance study established that the SMAD proteins physically interacts with CHIP. Further, another group observed that the overexpression of CHIP mediates downregulation of SMAD proteins and results in inhibition of BMP signaling.[100,267,381] Profilin-1 is an important mediator of actin polymerization and regulates the cellular migration. Lower expression of profilin-1 is correlated with several malignancies. In recent study, polyubiquitination and degradation of profilin-1 is studied in the CHIP overexpressed breast cancer cells which results in the enhancement of cellular migration and metastasis. Converse results were obtained upon CHIP knockdown.[382] Thus, all these reports indicate that CHIP may act like an oncogene by promoting metastatic hallmark of cancer. Subsequently, CHIP is found to increase cellular differentiation but not proliferation after the proteasome-mediated degradation of Menin.[384–386] In another finding, CHIP mediates degradation of LKB1 and causes increment in the cellular proliferation,[354,355,387] while TAp73α degradation causes anti-apoptotic action, and both finally leads to oncogenesis.[388] Thus, all these reports clearly suggest that CHIP can play as an oncogene in several cancers.

Significantly high expression of CHIP was found in a metastatic lymph nodes of esophageal squamous cell carcinoma (ESCC) in comparison to primary tumors observed by using a tissue microarray approach. Also, low expression level of CHIP was found with the better survival of ESCC cancer.[389] Similarly, CHIP expression level is higher in gall bladder tumor tissues with the overall decreased survival of gastric cancer patients.[390] A similar phenomenon is also observed in prostate cancer.[391] Hence, role of CHIP in different cancers is not that much straight forward to understand. Thus, much more study is needed to be done in this area for the deeper understanding of CHIP function in tumor biology.

Clinical significance and mechanistic details of CHIP in tumor biology

As reported in multiple cancerous tissues, CHIP expression level varies with type and grades of cancers. To inspect the variation of CHIP expression in different cancerous tissues, we screened almost every report published till December-2020 (Table 1). It was also found that tissues of breast cancer patients containing higher CHIP expression have higher overall survival rate than the patients having low expression level of CHIP.[375,392,393] On the other hand, the expression level of CHIP is up-regulated in postmenopausal breast cancerous tissues.[394] CHIP expression level in other cancerous tissues like gastric cancer,[58,361,395,396] human renal cell carcinoma[342,397] and non-small cell lung cancer[398] were found to be lesser as compared to the respective normal tissues. Other cancerous tissues like glioma,[399] gallbladder carcinoma,[390] HBV-hepatocellular carcinoma,[400] Head and neck cancer[401] and colorectal cancer tissues[364,402] were reported to have an increased CHIP expression level. So, we found that CHIP has wide diversity in its expression level and differential activity in different cancer scenario. Here, authors are interested to focus on the clinical significance and the mechanistic details of CHIP in tumor biology.

Glioma

Malignant gliomas are studied as an invasive, aggressive, and most common primary brain tumors, having median survival time of 12–15 months for glioblastoma and 2–5 years for anaplastic glioma.[403] In 2011, a research group has

Table 1 Expression of CHIP in various tumor tissues. Arrow headed (↑) and (↓) indicates up and down-regulation of CHIP.

Year	Type of Cancer	Number of samples	*In-vivo* study (Yes/No)	CHIP Expression	Reference
2010	Breast cancer	160	No	↓	375
2011	Breast cancer	183	No	↓	392
	Glioma	40	Yes	↑	399
2012	Gastric cancer	53	No	↓	395
2013	Esophageal squamous cell carcinoma	234	No	No change	389
	Gastric cancer	640	Yes	↓	396
	Gallbladder carcinoma	78	No	↑	390
	Colorectal cancer	320	No	↓	364
2015	HBV-hepatocellular carcinoma	79	No	↑	400
	Human renal cell carcinoma	304	Yes	↓	397
	Human renal cancer	12	Yes	↓	342
	Gastric cancer	164	No	↓	58
2016	Non-small cell lung cancer	106	Yes	↓	398
	Postmenopausal breast cancer	272	No	↑	394
2017	Head and neck cancer	101	Yes	↑	401
2018	Colorectal cancer	93	Yes	↑	402
	Prostate cancer	90	No	↑	391
2019	Gastric cancer	100	Yes	↓	361
	Breast cancer	128	Yes	↓	393

studied the CHIP expression level in 40 glioma patient samples. Among the various histological grades of glioma, authors found increase in CHIP expression level. The enhancement of colony formation and proliferation upon CHIP overexpression, while the knockdown of CHIP gives converse results in U87 and U251 glioma cell lines. Furthermore, intra-tumoral injection of CHIP shRNA containing lentiviral particles reduced the tumor size in tumor xenografts model, while opposite results were obtained after injecting CHIP overexpressed lentiviral particles. Thus, this pioneer report demonstrated that CHIP might have a tumorigenic role in human glioma.[399] Furthermore, a report from our lab has demonstrated the tumor suppressive role of CHIP in glioma by degrading the proto-oncogenic transcription factor c-Myc through ubiquitin proteasome system. Here, we found that the N-terminal chaperone associated TPR domain of CHIP is responsible for interaction with c-Myc. Upon inhibition of HSP90 chaperone with 17-AAG, c-Myc protein level was decreased. Additionally, CHIP inhibits the transcriptional activity of c-Myc and results into reduction in malignant behavior of CHIP in C6 glioma cells, while knockdown of CHIP indicates opposite results. We demonstrated the molecular mechanism of its tumor suppressive role in glioma tumor biology.[374] These opposing reports suggests that CHIP may acts a tumor suppressor or as an oncogene in glioma tumor biology.

Breast cancer

Breast cancer is one of the most common type of malignancy in women globally where CHIP through UPS indulged in the regulation of breast cancer prognosis.[404] Till date, three clinical sample-based reports have been documented and found low expression of CHIP in breast tumor tissues than normal. Each research group concludes the overall variation in CHIP expression level. It is also noticed that breast cancer patients with increased expression of CHIP have higher overall survival rate.[375,392,393] On the other hand, in another study CHIP expression level was studied in 272 postmenopausal breast cancerous tissues and up-regulation of CHIP expression level was observed in comparison to normal tissues.[394] It is also reported that approximately 70% of primary breast cancer patients are ERα positive.[405,406] CHIP was documented to degrade the ERα upon geldanamycin induced HSP90 inhibition.[349,404,407,408] In addition to ERα, ErbB2 is also reported as a biomarker of breast cancer tissues. High expression of ErbB2 is also observed in 30% of primary breast cancer patients.[409–411] CHIP is involved in ubiquitination and degradation of ErbB2. HSP90 inhibition leads to dissociation of ErbB2 from HSP90 chaperone complex and possible shifting to the HSP90 related HSP70 chaperone. Unfortunately, HSP70 associated E3 ligase CHIP hijacks ErbB2 and promotes its ubiquitination and degradation.[173,320,392,412–415] In addition to ERα and ErbB2, nuclear factor-κB (NF-κB) plays its crucial role in breast cancer.[416,417] TNF receptor associated factor (TRAF) associated family proteins play important roles in the activation of NF-κB pathway. Upon CHIP knockdown in breast cancer cells, increment in TRAF2 protein level was observed along with enhanced invasiveness. But this enhanced invasiveness in CHIP knockdown breast cancer cells was significantly reduced upon NF-κB inhibition. Thus, these results suggest that CHIP is indulged in the regulation of TRAF2-NF-κB signaling pathway which leads cell invasion to metastasis in breast cancer.[60,362,418–420]

Prostate cancer

Prostate cancer is a second most cause of cancer associated deaths among the men in USA.[421] A research group screened 90 prostate cancer patient samples for CHIP expression profiling and found that CHIP is highly expressed in prostate cancer tissues compared to the normal sample.[391] Androgen

receptor (AR) is highly expressed in prostate cancer and has crucial roles in prostate cancer progression. Thus, targeting androgen receptor may be attractive therapeutic strategy against prostate cancer. Recently a research group has documented the molecular mechanism of CHIP mediated ubiquitination and degradation of androgen receptor. They also observed that AR and CHIP interacts with each other through HSP70 chaperone.[371,422,423] Furthermore, we established that CHIP degrades tumor suppressor protein PTEN in prostate cancer samples and cell lines. We also reported that TPR domain of CHIP is primarily responsible for interaction with PTEN. CHIP mediated down-regulation of PTEN activates the PI3K/AKT pathway that leads to enhanced proliferation and survival of prostate cancer cells.[172] Thus, CHIP plays its dual role as a tumor suppressor as well as an oncogene in prostate tumor biology.

Gastric cancer

Most of the gastric cancer patients are diagnosed at advanced stages when tumor cells are resistant to radiotherapy and chemotherapy.[424] Long time ago, a research group performed clinical sample-based CHIP expression profiling study and documented the association of reduced CHIP expression with aggressive gastric cancer phenotype and also observed the disappearance of CHIP expression in patients with high lymph node invasion. They also observed increased expression of CHIP in moderately differentiated gastric cancer samples compared to the poorly differentiated gastric cancer samples.[395] Various other reports have been documented with CHIP expression profiling in variable gastric cancer samples[58,364,395,402] (Table 1). Low CHIP expression in 100 gastric cancer patient samples was reported recently in 2019.[361] Thus, from the above discussion it may be designated that CHIP may indulged in gastric cancer progression and can also serves as a significant diagnostic biomarker in gastric cancer patients.

Gallbladder carcinoma

Gallbladder carcinoma is typically diagnosed at later stages and is signified as a fatal disease.[425] Despite of surgical resection, 10–30% of gallbladder carcinoma patients have survival rate of 5 years.[426,427] Cyclooxygenase-2 and HIF are two molecular biomarkers of gallbladder carcinoma.[428] CHIP expression profiling was done using 78 gallbladder carcinoma patient samples, found increased CHIP expression in carcinoma samples in comparison to normal gallbladder tissues and nicely demonstrated the relationship of CHIP expression level with clinico-pathological characteristics and patient survival rate.[390] Retrospective investigations with large number of sample size are needed to be done, to understand the exact role of CHIP in gallbladder tumor biology.

Esophageal squamous cell carcinoma (ESCC)

ESCC is responsible for most of the esophageal malignant tumors, designated as most common cancer worldwide.[429] To establish a molecular biomarker of ESCC, a research group has demonstrated the relationship between CHIP expression level and ESCC. They observed no significant change in CHIP expression level in ESCC primary tumors and normal epithelial tissue but increased level in ESCC metastatic lymph nodes. The higher CHIP expression in metastatic lymph nodes was found to be a prognostic factor which is not favorable in stage-III ESCC patients. CHIP expression level may represent a significant prognostic molecular biomarker in metastatic lymph nodes in ESCC.[389]

No definite mechanism is established yet for its dichotomous role in any type of cancer. As discussed above in different cancers, CHIP may act as a novel therapeutic target or a diagnostic molecular biomarker. Role of CHIP varies from one type to another type of cancer. Literature review suggests that it may act as tumor suppressor or as an oncogene or even both in same cancer type with individual perspectives. Its role is totally unpredicted and solely depends upon downstream targets.

Therapeutic perspectives

Significance of CHIP has been studied in several pathological conditions such as neurological disorders (*viz.*, Parkinson's, Alzheimer's, Huntington's, Lafora, Atherosclerosis, Spino-cerebellar ataxia type-1 and hypo-gonadism), cardiac disorders, oxidative stress, muscular dystrophies, hyperthermia, bone related disorders and in cancer.[27] Now a days, cancer is one of the prominent, non-curable and life-threatening disease.[200,319,430] Till date, there is no definite, curable and life-saving strategy in cancer therapy.[431,432] Furthermore, as reported till date, CHIP has its anti-tumorigenic effects by ubiquitination and degradation of several target onco-proteins in different cancers. Subsequently, it has been found that CHIP overexpression is negatively correlated with tumor growth in multiple cancers such as breast cancer and gastric cancer.[58,278–280] Thus, CHIP overexpression leads to the inhibition of cancerous growth. Small molecule inhibitor of HSP90 also has anti-tumorigenic effect *via* stimulating the CHIP mediated degradation of oncoproteins. The reported HSP90 inhibitors in clinical trials are geldanamycin,[433] 17AAG,[434–462] 17DMAG,[442,463–467] AT13387,[468–474] AUY922,[475–485] BIIB021,[486,487] BIIB028,[488] Debio0932,[489] HSP990,[490] IPI-504,[491–493] KW2478,[494,495] SNX5422,[496–500], STA9090,[501–516] PU-H71,[517,518] TAS-116,[519], NVP-BEP800,[520] CUDC 305,[521], TQB3474,[522] PEN8667,[523] RTA-901 [524] and XL888 [525,526] (Fig. 6). All these compounds have tumor growth inhibitory property when used alone or in combination with standard anticancer drugs for clinical advancement (Table 2). These compounds act by blocking the ATP binding site of HSP90 which leads to CHIP mediated degradation of oncogenic client proteins results in an anti-tumorigenic effect.[527] The details of clinical advancement of these inhibitors during the period 2005–2021 are presented in Table 2. Thus, inhibition of HSP90 in combination with over-expression of CHIP may be an alternate novel and ideal anti-cancer strategy for cancer therapy.

Basic disputes and unresolved mysteries of CHIP

In last two decades, CHIP has been established as a distinct protein enzyme which has huge number of substrates. CHIP

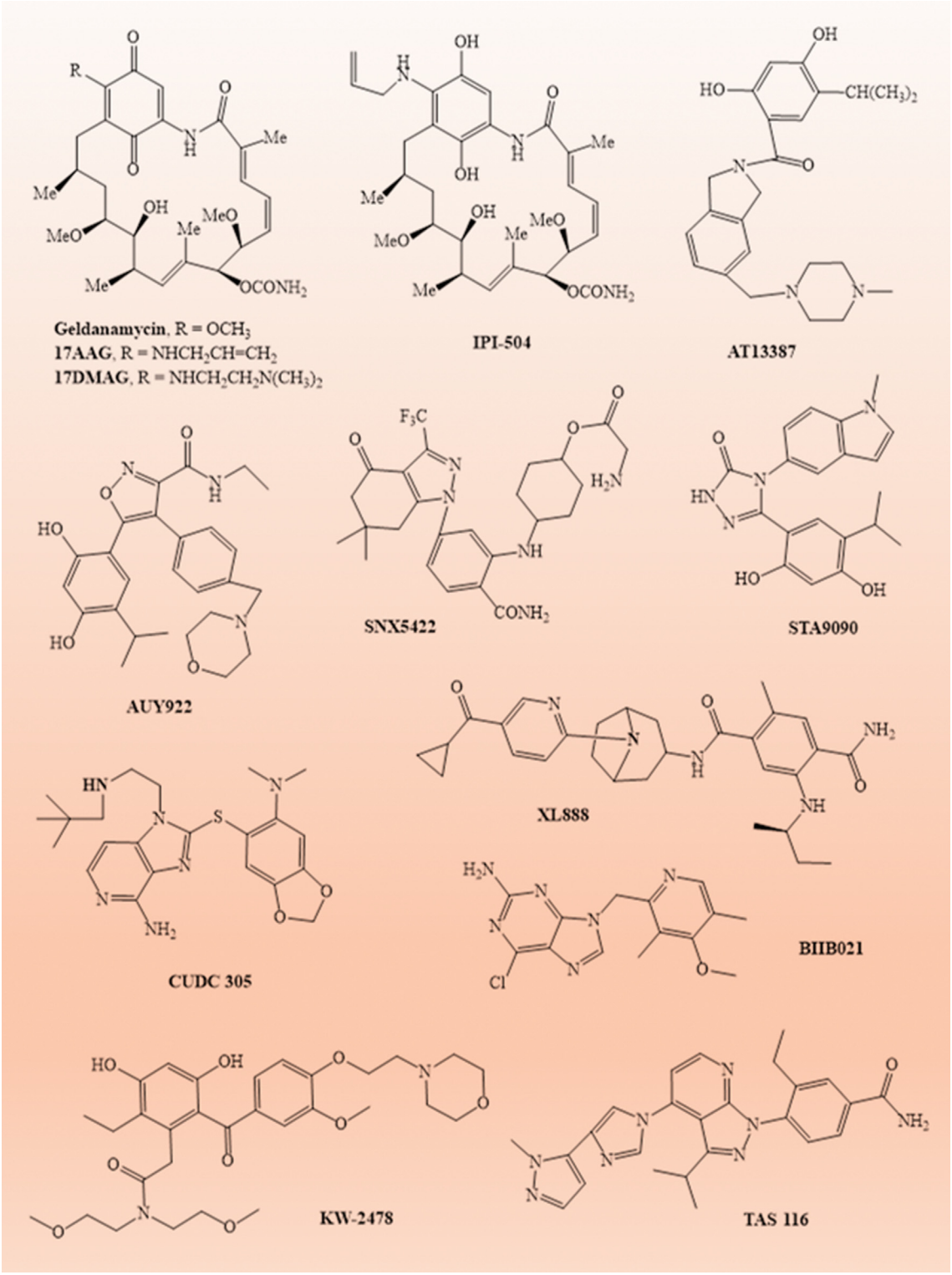

Figure 6 Chemical structures of HSP90 inhibitors. Figure depicts the chemical structures of various HSP90 inhibitors *viz.*, geldanamycin, 17AAG, 17DMAG, IPI-504, AT13387, AUY922, SNX5422, STA9090, XL888, CUDC 305, BIIB021, KW-2478 and TAS-116, act as anti-cancer agents. All the structures were drawn by using chem draw software.

interacts with its substrates through direct or indirect manner and performs a key role in various cellular processes such as apoptosis, proliferation, metabolism and in cellular signaling. In various reports, it is observed that CHIP regulates the substrate proteins in a chaperone dependent as well as in independent manner. It is still a key question to study how CHIP interacts with proteins and the selectivity in the complex cellular proteome. Further, it is

Table 2 Clinical advancement of HSP90 inhibitors for cancer therapy in a combinatorial approach.

HSP90 inhibitor	Year	Combination	Clinical status (Phases)	NCT no.	Status	Outcome/Indication	References
17AAG	2005		I	NCT00003969	C	Advanced cancer	434
			I	NCT00003969	C	Advanced cancer	435
			I	NCT00003969	C	Advanced malignancy	436
			I	NCT00003969	C	Solid tumors	437
	2006		I	NCT00003969	C	Advanced cancer	438
			II	N/A	—	Renal cell carcinoma	439
	2007		I	NCT00003969	C	Advanced cancer	440
		Trastuzumab	I	N/A	—	HER2-positive BC	441
			I	NCT00003969	C	Advanced cancers	442
			I	NCT00079404	C	Pediatric solid tumors	443
			I	NCT00079404	C	Pediatric solid tumors	444
	2008	Irinotecan	I	NCT00119236	C	Solid tumors	445
			II	NCT00118092	C	Prostate cancer	446
			II	NCT00104897	C	Metastatic melanoma	447
		Paclitaxel	I	NCT00087217	C	Solid tumors	448
	2010	Bortezomib	II	N/A	—	Multiple melanoma	449
		Sorafenib	I	NCT00121264	C	Solid tumors	450
			I	NCT0051437/NCT00546780	C	Multiple myeloma	451
		Gemcitabine or cisplatin	I	NCT00047047	C	Solid tumors	452
	2011	Trastuzumab	II	NCT00773344	C	HER2-positive BC	453
		Cytarabine	I	NCT00098423	C	Acute leukemia	454
		Docetaxel	I	NCT00058253	C	Solid tumors	455
		Gemcitabine	II	NCT00093496	C	EPC and PPC	456
		Bortezomib	I/II	NCT00514371	C	Multiple myeloma	457
	2012		II	N/A	—	Breast cancer	458
			II	NCT00104897	C	Metastatic melanoma	459
	2013	Bortezomib	I	NCT00096005	T	Solid malignancies	460
		Bortezomib	I	N/A	—	AML	461
	2015	Gemcitabine	II	NCT00577889	C	Pancreatic cancer	462
17-DMAG	2010		I	NCT00089362	C	Solid tumors	442
			I	NCT00088868	C	Advanced malignancy	463
			I	NCT0008927/NCT00088868	C	AML	464
	2011		I	NCT00248521	U	Solid tumors	465
	2012	Trastuzumab	I	N/A	—	Solid tumors	466
	2016		I	NCT01126502	W	CLL/ALL	467
AT13387	2015		I	NCT01246102	C	Solid tumors	468
			I	NCT00878423	C	Solid tumors	469
	2016	Talazoparib	I	NCT02627430	W	Ovarian cancer, FTC, PPC, TNBC	470
	2021	AT7519	I	NCT02503709	A	Solid tumors	471
		Olaparib	I	NCT02898207	A	Ovarian cancer, FTC, PPC and TNBC	472
		Cisplatin and radiation	I	NCT02381535	A	SCC of the head and neck	473

(*continued on next page*)

Table 2 (*continued*)

HSP90 inhibitor	Year	Combination	Clinical status (Phases)	NCT no.	Status	Outcome/Indication	References
		Paclitaxel	I	NCT02474173	A	TNBC	474
AUY922	2013		I	N/A		Solid tumors	475
	2014	89Zr-trastuzumab/bevacizumab	I	NCT01081613/NCT01081600	C	Breast cancer	476
	2015	Bortezomib	I/Ib	NCT00708292	C	Multiple myeloma	477
		Capecitabine	I	NCT01226732	C	Solid tumors	478
	2016		II	NCT01404650	C	GIST	479
			II	NCT01124864	C	NSCLC	480
			II	NCT01668173	T	MPNs	481
	2017		II	NCT01485536	T	Lymphoma	482
	2019		II	NCT01646125	T	NSCLC	483
		Erlotinib	I/II	NCT01259089	C	Lung ADC, NSCLC	484
	2020	Pemetrexed	I	NCT01784640	C	NSCLC, lung cancer	485
BIIB021	2013		II	NCT00618319	C	GIST	486
	2014		I	NCT00618735	C	Solid tumors	487
BIIB028	2013		I	NCT00725933	C	Solid tumors	488
Debio0932	2015		I	NCT01168752	C	Advanced cancer	489
HSP990	2015		I	NCT00879905	C	Solid tumors	490
IPI-504	2011		I	NCT00113204	C	Multiple myeloma	491
	2013		I	NCT00276302	C	GIST and sarcomas	492
	2017		II	NCT01228435	T	Lung cancer	493
KW-2478	2014	Bortezomib	I/II	NCT01063907	C	Multiple melanoma	494
	2016		I	NCT00457782	C	B-cell malignancy	495
SNX-5422	2011		I	NCT00647764	C	ST's and lymphomas	496
	2013		I	NCT00595686	C	Malignant hematology	497
	2017		I/II	NCT01848756	T	HER2 positive cancers	498
	2018		II	NCT02612285	T	TP53 null cancers	499
	2019	Lbrutinib	I	NCT02973399	T	CLL	500
STA-9090	2013		I	NCT00687934	C	Solid tumors	501
			II	NCT01562015	C	Advanced NSCLC	502
	2014		II	NCT01111838	C	Metastatic CRC	503
			II	NCT01227018	T	Pancreas cancer	507
	2015	Docetaxel	II	NCT01348126	T	Advanced NSCLC	504
	2016		II	NCT01270880	C	Prostate cancer	505
			I	NCT02334319	T	Head and neck cancer	508
		Paclitaxel	II	NCT02637375	W	Breast cancer	509
	2017		II	NCT01551693	T	Melanoma	510
	2018		II	NCT01200238	C	Ocular melanoma	511
		Paclitaxel/Trastuzumab	I	NCT02060253	C	HER2-positive BC	512
		Ziv-aflibercept	I	NCT02192541	T	UC, GIST & NSCLC	513
	2019		II	NCT01173523	C	SCLC	514
			I/II	NCT02012192	T	EPC, FTC and PPC	515

	Sirolimus	I/II	NCT02008877	C	MPNST, sarcoma	516
	2020 Docetaxel	III	NCT01798485	T	NSCLC	506
PU-H71	2017	I	NCT01581541	T	ST's, lymphoma	517
	2020 Ruxolitinib	I	NCT03935555	R	PMF, Post-PV MF, Post-ET MF	518
TAS-116	2019	I	NCT02965885	C	Solid tumors	519
NVP-BEP800	2020	—	NCT04437420	R	T-ALL, B-ALL	520
CUDC 305	2019	I	NCT03675542	R	Psoriasis vulgaris	521
TQB3474	2019	I	NCT04144855	R	Solid tumors	522
PEN-866	2021	I/II	NCT03221400	R	Solid tumors	523
RTA-901	2017	I	NCT02666963	C	Healthy adults	524
XL888	2020 Pembrolizumab	I	NCT03095781	R	GIST	525
	2021 Vemurafenib /Cobimetinib	I	NCT02721459	A	Melanoma	526

Abbreviations C: Completed; T: Terminated; R: Recruiting; U: Unknown; A: Active; W: Withdrawn; N/A: Not available; CLL: Chronic lymphocytic leukemia; SLL: Small lymphocytic lymphoma; NSCLC: Non-small cell lung cancer; GIST: Gastrointestinal stromal tumors; T-ALL: T-cell acute lymphocytic leukemia; B-ALL: B-cell acute lymphocytic leukemia; PMF: Primary myelofibrosis; Post-PV MF: Post-polycythemia vera myelofibrosis; Post-ET MF: Post-essential thrombocythemia myelofibrosis; MPNST: Malignant peripheral nerve sheath tumor; SCLC: Small cell lung cancer; TP53: Tumor protein P53; TNBC: Triple negative breast cancer; SCC: Squamous cell carcinoma; CRC: Colorectal cancer; MPNs: Myeloproliferative neoplasms; EPC: Epithelial ovarian cancer; FTC: Fallopian tube cancer; PPC: Primary peritoneal cancer; BC: Breast cancer; AML: Acute myloid leukemia; ST's: Solid tumors; UC: Urothelial carcinoma; Lung ADC: Lung adenocarcinoma.

found that chaperones are involved in recruitment of several proteins for folding or CHIP mediated ubiquitination and degradation. Still, a doubt remains to be resolved whether other auxiliary factors like co-chaperones are involved in the substrate selection for recruitment under diseased context. Both TPR and Ubox are structural domains of CHIP, responsible for determining its functional abilities. As reported, CHIP helps in binding the ubiquitin molecule to the substrate proteins. Although, it seems to be some specific known sequence elements for CHIP mediated ubiquitination of substrates, this question is not yet answered. Additionally, CHIP is responsible for its dual actions as a co-chaperone as well as for E3/E4 ligase activity. It is a subject of study, how CHIP decides to perform its dual role inside the cells. How CHIP along with other chaperones acknowledge mis-folded proteins to be degraded, is still a crucial question to be answered. Thus, several studies needed to be conducted in this direction, for better understanding of the probable ways to pick up cellular proteins upon the background of organizational and physiological situations. Number of studies have been performed to distinguish the normal proteins from the misfolded ones, whether they are to be altered or degraded. Significant answers have not yet been found according to our current knowledge. CHIP also has its decisive roles in maintenance of cellular homeostasis and serves as a safety guard from the stress induced various diseases. Till date, major research on CHIP was focused upon its role but critical investigation about its disease specific differential regulation and gene expression is yet to be confirmed. It is urgent now to study about how and in which conditions CHIP is acting like a dual agent *viz.* tumor suppressor and oncogene. Thus, much work is needed to be done to resolve all these unresolved mysteries about CHIP for future perspectives.

Conclusion

CHIP acts as a central player in the multiple cellular processes including apoptosis, immunity, stress-response, inflammation, protein trafficking and morphogenesis. Its role has been convincingly studied in numerous morbid condition such as neurological disorders, cardiac diseases, bone remodeling and in cancer. Several studies indicate that CHIP can act as a dual agent like tumor suppressor as well as an oncogene in tumor biology. Furthermore, in multiple reports CHIP also manifests its defensive role by helping cells to remove deleterious forms of several proteins, especially under stress situation. Also, recent studies suggest that CHIP may be a novel therapeutic target to remove the numerous onco-proteins in multiple cancers. Thus, CHIP over-expression in combination with nano-encapsulated HSP90 inhibitors seems to be a valuable combinatorial strategy for next generation cancer therapy.

Author contributions

Conceived the idea and review structure: SK, MB and MKG; Wrote the manuscript: SK and MKG; Revised the manuscript: MB and MKG. All authors have read and agreed to the final draft of the manuscript.

Conflict of interests

There is no competing interest.

Funding

This work is jointly supported by the Department of Science and Technology (NanoMission: DST/NM/NT/2018/105(G); SERB: EMR/2017/000992) and HCT-Focused Basic Research (FBR), (Sanction No. 31-2(274)2020-21/Bud-II, dated-03.03.2021), CSIR, Govt. of India.

Acknowledgements

Authors are happy to acknowledge Ms. Pratyasha Ghosh, Department of Economics, Bethune College, University of Calcutta for carefully editing the manuscript.

Abbreviations

ADP	Adenosine di-phosphate
AhR	Aryl hydrocarbon receptor
AIF	Apoptosis inducing factor
AMPK	AMP-activated protein kinase
AR	Androgen receptor
ASK1	Apoptosis signal-regulating kinase 1
ATP	Adenosine tri-phosphate
BACE1	Beta-secretase 1
BAG 1, 2 and 3	BCL2 associated athano-Gene 1, 2 and 3
BER	Base excision repair
BMAL-1	Brain and muscle ARNT-Like 1
CARMA1	Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1
CASA	Chaperone assisted selective autophagy
CDK4	Cyclin-dependent kinase 4
CFTR	Cystic fibrosis transmembrane conductance regulator
ChAT	Choline acetyltransferase
CHIP	Carboxy-terminus of Hsp70-interacting protein
CK2β	Casein kinase protein subunit 2β
CLEC-II	C-type lectin-like type II transmembrane receptor
ClpP4	Chloroplast protease subunit P4
CMA	Chaperone-mediated autophagy
CtBP2	C-terminal-binding protein 2
C-ErbB2/Neu	Receptor tyrosine-protein kinase erbB-2
DDIAS	DNA Damage Induced Apoptosis Suppressor
DLK	Dual leucine zipper kinase
DNA	Deoxy-ribose nucleic acid
E1's	Ubiquitin activating enzymes
E2's	Ubiquitin conjugating enzymes
E3's	Ubiquitin ligase enzymes
EGFR	Epidermal growth factor receptor
Endo G	Endonuclease G
ER	Endoplasmic reticulum
ERα	Estrogen receptor alpha
ERKs	Extracellular-signal-regulated kinase
EZH2	Enhancer of zeste homolog 2
eIF4E	Eukaryotic translation initiation factor 4E
eIF5A	Eukaryotic translation initiation factor 5A
FADD	FAS-associated *via* death domain
FGFR3	Fibroblast growth factor receptor 3
FMR1	Fragile X mental retardation 1
FOXO1	Forkhead box protein O1
Foxp3	Forkhead box P3
GHR	Growth hormone receptor
GHS	Gorden holmes syndrome
GR	Glucocorticoid receptor
Gαs	G_s alpha subunit
HIV	Human immunodeficiency virus
HECT	Homologous to the E6-AP carboxyl terminus
HDAC6	Histone deacetylase 6
HERG	human Ether-à-go-go-Related Gene
HIF1α	Hypoxia inducible factor-1 alpha
HIP	Hsp70-interacting protein
HIPK2	Homeodomain-interacting protein kinase 2
HOP	Hsp70-Hsp90 organizing protein
HSP70, 40, 72, 40 and 90	Heat shock protein-70, 40, 72, 40 and 90
H_2O_2	Hydrogen peroxide
hPXR T408D mutant	Phosphomimetic mutation at threonine-408
hTERT	human Telomerase reverse transcriptase
IA	Intracranial aneurysm
ICER	Inducible cAMP Early Repressor
IL-4α	Interleukin 4
IRE1	Inositol-requiring enzyme 1
IRF-1	Interferon regulatory factor 1
IRS4	Insulin receptor substrate 4
ISG15	Interferon-stimulated gene 15
JNK	C-jun N-terminal kinase
KCNQ4	potassium voltage-gated channel subfamily KQT member 4
LKB1	liver kinase B1
LRRK2	Leucine rich repeat kinase 2
MAPK3	Mitogen-activated protein kinase 3
MAST1	Microtubule-associated serine/threonine-protein kinase 1
MEKK	Mitogen-activated protein kinase kinase
MIF	Migration inhibitory factor
MJD	Machado-joseph disease
MLK3	Mixed-lineage kinase-3
MLK4β	Mixed lineage kinase 4β
MZF1	Myeloid Zinc Finger 1
mHtt	Mutant Huntington
Niemann-Pick C1	Niemann-pick disease, type C1
NIK	NF-κB-inducing kinase

NEK10	NIMA related kinase 10
NFATc3	Nuclear factor of activated T-cells, cytoplasmic 3
NOX4	NADPH oxidase 4
NPM-ALK	Nucleophosmin-Anaplastic lymphoma kinase
NQO1	NAD(P)H dehydrogenase [quinone] 1
NUCB1	Nucleobindin 1
OCT4	Octamer-binding transcription factor 4
OTUD1	OTU Deubiquitinase 1
PABPN1	Poly(A) binding protein nuclear 1
Pae1R	Parkin associated endothelin like receptor
PINK1	PTEN-induced kinase 1
PI3K	Phosphoinositide 3-kinase
PKC-ζ/SRC	Protein kinase C, zeta type
PKM2	Pyruvate kinase M2
PolyQ	Polyglutamine tract
PRMT1,15	Protein arginine methyl-transferase 1, 15
PrPC	Cellular Prion Protein
PPARγ	Peroxisome proliferator-activated receptor γ
PTK6	Protein Tyrosine Kinase 6
PTEN	Phosphatase and tensin homolog
p65	Transcription factor p65 (RELA)
p38MAPK	p38 mitogen-activated protein kinases
p42 Ebp1	Tumor suppressor p42, ErbB3-binding protein 1
phosphatase PPP3CA	Serine/threonine-protein phosphatase 2B catalytic subunit alpha
RHBDF2	Rhomboid 5 Homolog 2
RFX-1	Regulatory factor X-1
RIG-1	Retinoic acid-inducible gene I
RING	Really interesting new gene
RIPK3	Receptor-interacting serine/threonine-protein kinase 3
RNF216	Ring finger protein 216
RUNX 1 and 2	Runt-related transcription factor 1 and 2
SCAR16	Spinocerebellar ataxia autosomal recessive type 16
SENP3	Sentrin/SUMO-specific protease
SOD2	Superoxide dismutase 2
SGK1 and 3	Serum/glucocorticoid regulated kinase 1 and 3
SirT6	Sirtuin 6
SHP-1	Src homology region 2 domain-containing phosphatase-1
SMAD 1 and 3	Small mothers against dpp 1 and 3
SNPH	Syntaphilin
SRC-3	Steroid receptor coactivator-3
STAT4	Signal transducer and activator of transcription 4
STUB1	STIP1 homology and Ubox containing protein 1
Tat	Trans-activator of transcription
TAL1/Scl	stem cell leukemia/T-cell acute lymphoblastic leukemia 1
TAp73α	p73α antibody specifically recognizes human and monkey full-length p73α (TAp73α) protein
TEAD4	TEA Domain Transcription Factor 4
TFEB	Transcription factor EB
TLR	Toll-like receptor
TNFα	Tumor necrosis factor alpha
TPR	Tetratricopeptide
TRAF3	TNF receptor-associated factor 3
UPS	Ubiquitin proteasome system
XRCC1	X-ray repair cross complementing group-1
17AAG	17-N-allylamino-17-demethoxygeldanamycin
17DMAG	17-Dimethylaminoethylamino-17-demethoxygeldanamycin
β-APP	β-amyloid precursor protein
(i, n, e)NOS	(inducible, neuronal, endothelial) Nitric oxide synthase

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2021.08.003.

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