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Cdc37 as a Co-chaperone to Hsp90

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Abstract

The co-chaperone p50/Cdc37 is an important partner for Hsp90, assisting in molecular chaperone activities, particularly with regard to the regulation of protein kinases. The Hsp90 / Cdc37complex controls the folding of a large proportion of protein kinases and thus stands at the hub of a multitude of intracellular signaling networks. Its effects thus reach beyond the housekeeping pathways of protein folding into regulation of a wide range of cellular processes. Due to its influence in cell growth pathways Cdc37 has attracted much attention as a potential intermediate in carcinogenesis. Cdc37 is an attractive potential target in cancer due to: (1) it may be expressed to high level in some types of cancer and (2) Cdc37 controls multiple signaling pathways. This indicates a potential for: (1) selectivity due to its elevated expression and (2) robustness as the co-chaperone may control multiple growth signaling pathways and thus be less prone to evolution of resistance than other oncoproteins. Cdc37 may also be involved in other aspects of pathophysiology. Protein aggregation disorders have been linked to molecular chaperones and to age related declines in molecular chaperones and co-chaperones. Cdc37 appears to be a potential agent in longevity due to its links to protein folding and autophagy and it will be informative to study the role of Cdc37 maintenance / decline in aging organisms.

Keywords

Cdc37; co-chaperone; Hsp90; protein kinase; cancer; autophagy

Introduction

Folding of many proteins in the cell to a fully functional conformation requires the influence of molecular chaperones (Ellis 2007). Such molecules appear to be required to inhibit the formation of alternatively folded conformations that lack canonical gene function, and permit the majority of the translated protein to assume its functional shape. It is now accepted by many that molecular chaperones play essential roles in cellular pathology as well as in normal function and roles for chaperone overexpression in tumorigenesis and tumor progression have been described while failure in chaperone function may underlie processes in aging (Ciocca and Calderwood 2005, Calderwood, Murshid et al. 2009, Jinwal, Abisambra et al. 2012, Ciocca, Arrigo et al. 2013). The underlying causes of increased chaperone expression in cancer and loss of chaperone activity in aging have not currently

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been deduced. It has been assumed that elevated amounts of proteins with or without oncogenic mutations accumulate in cancer increasing the “folding burden placed on cancer cells (Calderwood and Gong 2012). However direct proof for such a hypothesis is required. It is known that chaperones such as Hsp27, Hsp70 and Hsp90 often undergo enhanced expression during cancer development and play roles in many of the key steps in cancer development such as acquisition of independent growth, escape from oncogene mediated programmed cell death and senescence, *de novo* angiogenesis invasion and metastasis (Ciocca and Calderwood 2005, Calderwood, Khaleque et al. 2006). This may point to key regulatory roles for the chaperones in cancer. In addition Hsp27, Hsp70 and Hsp90 are all regulated at the transcriptional level primarily by heat shock factor 1 (HSF1) a protein that responds to both stress and cancer signals, leading to potent HSP synthesis and enhanced tumorigenesis (Santagata, Hu et al. 2011, Ciocca, Arrigo et al. 2013). Interactions between HSF1 and Hsp90 are particularly intriguing, as transcriptional activation of HSF1 leads to Hsp90 increases, while Hsp90 is a potent HSF1 repressor, a tautology with some significance in cellular responses to Hsp90 targeting drugs(Zou, Guo et al. 1998, Boellmann, Guettouche et al. 2004). Many members of the molecular chaperone family require accessory proteins known as co-chaperones in order to function at significant rates in cells (Calderwood 2013). Co-chaperones may be decisive in the selection of Hsp90 clients within the cell and may determine the rate of polypeptide folding and the ability of chaperones to stably interact with unstable proteins(Cox and Johnson 2011). Optimal Hsp90 activity involves a wide range of co-chaperones including Sgt1, p23, Aha1, Cdc37, Hop, Cyp40, FKBP1, FKBP2, PP5 phosphatase, TTC4, TTC5 and XAP2 which regulate the chaperoning cycle as well as function and localization in the cells (Cox and Johnson 2011, Calderwood 2013). The subject of the current review is the Hsp90 co-chaperone role of Cdc37.

As would be surmised from its name, the *CDC37* gene was discovered in a screen for cell division cycle genes in S. *cereviseae* (Reed 1980). It has since been shown to be conserved to man, although Cdc37 homologs in plants have not been reported. Despite its discovery in a cell cycle screen, the Cdc37 protein apparently does not perform a traditional cell cycle checkpoint role, such as has been attributed to the cyclins and cell division kinases (cdk), and instead appears to function largely by enhancing the stability and activities of protein kinases, including cdks (Pearl 2005, Caplan, Ma’ayan et al. 2007, Caplan, Mandal et al. 2007). Cdc37 has emerged as a co-chaperone that is required for the stable folding of a wide spectrum of protein kinases when complexed with Hsp90 and has thus emerged as an important signal transduction molecule (Caplan, Ma’ayan et al. 2007, Gray, Prince et al. 2008). Indeed recent proteomic studies confirmed that Hsp90 interacted with a wide range of kinases and that the majority of these interactions were shared with Cdc37 (Taipale, Krykbaeva et al. 2012). This was in contrast with the findings regarding transcription factors, including steroid hormone receptors, only a few of which proteins seemed to interact significantly with Hsp90 or Cdc37 (Taipale, Krykbaeva et al. 2012). Hsp90 has been shown to bind to client proteins and lead to their optimal folding in a series of reactions that can be regarded as involving a cycle of ATP-dependent conformational changes within the Hsp90 molecule (Fig. 1)(Taipale, Jarosz et al. 2010, Cox and Johnson 2011, Calderwood 2013). Hsp90 carries out its molecular chaperone functions as a dimer. Such Hsp90 dimers bind to the client while in an open conformation and then are converted to a more closed

conformation on binding of ATP, a conformation in which substrates are tightly bound. The exact nature of the Hsp90-client binding interaction is however still somewhat obscure. Release of bound, folded client proteins from the Hsp90 involves ATP hydrolysis, a reaction that leads to loss of affinity for the client protein (Fig. 1). Cdc37 binding to Hsp90 appears to inhibit this latter ATPase activity of Hsp90 and to permit prolonged interactions between chaperone and client (Fig. 1)(Cox and Johnson 2011). During the interaction with Hsp90, Cdc37 binds both to the client kinase as well as to hsp90 itself and both interactions are required for chaperone function (Gray, Prince et al. 2008). Cdc37 binds to the highly conserved N-loop of protein kinases and is thought to stabilize the aC-b4 loop, while Hsp90 binds both the N and C lobes (Discussed in more detail in Gray et al, 2008)., Two distinct client interaction domains have been described in mammalian Cdc37, including a conserved N-terminal domain as well as a C terminal domain that is not conserved in yeast Cdc37 (Calderwood 2013). Thus Cdc37 is a molecular chaperone itself that, at least in Yeast appears to have independent protein interaction functions but that in mammalian cells more commonly operates in cooperation with Hsp90 to optimally fold the structures of protein kinases (MacLean and Picard 2003, Turnbull, Martin et al. 2005). Cdc37 has been shown to bind to the catalytic domains of a large number of client kinases, structures that appear to be conserved in all protein kinases suggesting a common mode of interaction with a range of such enzymes (Vaughan, Gohlke et al. 2006, Caplan, Ma'ayan et al. 2007, Taipale, Krykbaeva et al. 2012). However, such Cdc37-kinase interactions are by no means uniform in nature. For instance Hsp90-Cdc37 complexes are required to maintain Cdk4 in folded conformation only until such kinases encounter the regulatory Cyclin D1 subunits when they then become chaperone-independent rev. (Caplan, Ma'ayan et al. 2007). The oncogenic receptor tyrosine kinase ERBB2 by contrast requires persistent association with Hsp90-Cdc37 complexes for stability and activity (Caplan, Ma'ayan et al. 2007). Indeed quantitative studies of Hsp90/Cdc37 complex / kinase client interactions show that even closely related kinase family members interact with quite different affinities. Another principle involved in Cdc37 / client interactions seems to be that the chaperone complex binds most avidly to the more unstable protein kinases and stabilization of clients led to reduced association (Taipale, Krykbaeva et al. 2012). In addition, it has been shown that the exchange of ATP in activated kinase clients during enzymatic activity leads to their increased instability and enhanced chaperone binding (Gray, Prince et al. 2008). Interestingly, but in accordance with the prior statements, it would appear that protein kinase catalytic activities may be reduced under Cdc37 / Hsp90 complex-bound conditions, as determined for the LKB1 kinase (Taipale, Krykbaeva et al. 2012). Dissociation of LKB1 from the Cdc37 / Hsp90 complex led to transient activation of kinase activity prior to degradation via a pathway involving association with Hsp70 family proteins, recruitment of ubiquitin ligase CHIP and breakdown in the proteasome (Xu and Neckers 2012).

Posttranslational modifications of Cdc37 and Hsp90

The Hsp90 / Cdc37 interaction is also regulated by posttranscriptional modifications (PTM) that affect profoundly the chaperoning cycle. Both proteins appear to be substrates for casein kinase 2 (CK2), an enzyme that is in fact also a client (Miyata and Nishida 2005). CK2 phosphorylates Cdc37 on serine 13, a modification with profound impact on function,

leading to formation of stable complexes with the clients (Miyata and Nishida 2005). I addition CK2 phosphorylates Hsp90 on threonine (T) 22 in yeast (human T36), an interaction that stabilizes binding to co-chaperones Cdc37 and Aha1 (Mollapour, Tsutsumi et al. 2011). CK2 is thus a key enzyme in Hsp90 / Cdc37 client folding. Recently it has been shown that tyrosine (Y) phosphorylation also has profound effects on Hsp90 / Cdc37 activities. Cdc37 phosphorylation on Y4 and Y298 disrupts client association while Hsp90 phosphorylation on Y197 leads to dissociation of Cdc37. (Xu, Mollapour et al. 2012, Xu and Neckers 2012) The enzyme implicated in these modifications is the non-receptor tyrosine kinase Yes (Summy, Sudol et al. 2003, Xu, Mollapour et al. 2012). The findings thus suggest profound regulation of each step of the Cdc37 / Hsp90 chaperoning cycle by PTMs.

Cdc37 in cell proliferation and cancer

As a cell cycle division protein, required to drive cell proliferation, it is probably not surprising that *CDC37* appears to play a positive role in tumorigenesis (Stepanova, Finegold et al. 2000, Gray, Prince et al. 2008). An early hint suggesting such a role was provided by the finding of a requirement for Cdc37, along with Hsp90 in the transforming functions of the viral oncogene p60v-src (Dey, Lightbody et al. 1996, Perdew, Wiegand et al. 1997). More conclusive evidence for a transforming role for Cdc37 was next provided by the finding that overexpression of the *cdc37* gene in transgenic mice could lead to elevated rates of prostate tumorigenesis, a process that was amplified by co-expression of the proto-oncogene c-Myc (Stepanova, Yang et al. 2000). Subsequently other cancer types such as anaplastic large cell lymphoma, acute myeloblastic leukemia, multiple myeloma and hepatocellular carcinoma have been shown to express high levels of cdc37 (rev.) (Gray, Prince et al. 2008). The exact upstream mediator of Cdc37 tumorigenesis might be currently difficult to tie down due to the large numbers of potential Hsp90 / CDc37 targets with potential roles in carcinogenesis. Probable candidates could include: (1) Activity of the androgen receptor (AR) (Heinlein and Chang 2004). While most steroid hormone receptors require Hsp90 for optimal folding and activity, only AR has been shown to be dependent on Cdc37 (Fliss, Fang et al. 1997, Rao, Lee et al. 2001). Indeed Cdc37 knockdown in AR+ LnCaP cells was shown to lead to the loss of androgen-dependent AR-mediated transcriptional activity and to a reduction in target PSA expression (Gray, Stevenson et al. 2007). It may be significant that Cdc37 has been found to be associated with the AR co-activating protein Vav3 (Wu, Peacock et al. 2013). Disruption of AR-Vav3 interactions inhibited the co-activating effects of Vav3 (Wu, Peacock et al. 2013). AR has been shown to be essential for the early stages in prostate tumorigenesis and to even play unpredicted roles in castration-resistant forms of PCa. Thus a role for Cdc37 in fostering AR activity and prostate carcinogenesis might be postulated. However other promising candidates for CDC37 targets exist. Protein kinases are the preferred clients of Cdc37 and upward of 50 % of kinases may require Cdc37 to a greater or lesser degree (Gray, Prince et al. 2008). It has been shown that the phosphatidyl inositol – 3 kinase (PI-3K) pathway plays a key driving role in prostate carcinogenesis and that the PI-3K inhibitory pathway, mediated through the lipid phosphatase PTEN inhibits this process (Bitting and Armstrong 2013). Indeed, inactivation of PTEN leads to spontaneous prostate carcinogenesis. It was also shown that knockdown of Cdc37 led to inhibition of Akt, the kinase directly downstream of PI-3K as

well as to inhibition of the S6 ribosomal protein, a substrate of the mTORC1 kinase complex, another enzyme regulated downstream of PI-3K (Gray, Stevenson et al. 2007). The mTORC1 pathway has been shown to play key roles in cancer progression by boosting the rate of translation and permitting elevated protein synthesis in cancer cells. Other potential Cdc37 dependent targets could include receptor tyrosine kinases such as EGFR and HER2/*neu* that are CDC37 clients and could also play roles in prostate cancer (Calderwood, S. K. et al, in preparation), (Lavictoire, Parolin et al. 2003). However, as there is currently no definitive proof for any of these pathways and other candidates such as no-receptor tyrosine kinases of the Src family as well as mutant or over-expressed KIT, MET, ALK and RAF could play roles.

Cdc37 and Cancer Treatment

The dependence of cancer, particularly prostate cancer cells, on Cdc37 suggests this molecule as a potential target. This approach would have the decided advantage of leading to multi-targeting and the potential for evasion of resistance in contrast to targeting individual oncoproteins, in which evolution of resistance is problematic. Cdc37 knockdown was shown to reduce proliferation to minimal levels in a range of malignant cell types (Gray, Stevenson et al. 2007, Gray, Prince et al. 2008, Smith and Workman 2009). A natural product-based drug has recently been isolated that can disrupt Hsp90 / Cdc37 interactions. This compound Celastrol could thus be envisaged as a potential drug for targeting Cdc37 activity in cancer (Salminen, Lehtonen et al. 2010). However, this compound is lacking in specificity, was shown to directly inhibit both IκκB kinase activity and the function of the proteasome and to induce HSF1 activity (Calderwood 2013). No doubt future endeavors will lead to further Cdc37-targeted drugs with higher specificity.

Roles for Cdc37 in autophagy and protein aggregation disorders

Unsurprisingly, with its versatile role in kinase activation, Cdc37 appears to plays roles in cell pathology outside of cancer. The Hsp90-Cdc37 complex appears to participate in the upstream activation of autophagy, one of the primary pathways in protein quality control and longevity (Calderwood, Murshid et al. 2009). Autophagy is significant in protein homeostasis in that bulky protein aggregates or damaged organelles that cannot enter the lumen of the proteasome for proteolytic digestion can be enveloped by autophagosomes and broken down (Calderwood, Murshid et al. 2009). The Cdc37-Hsp90 complex was shown to stabilizes and activate ULK1, a protein kinase that phosphorylates Atg1 one of the first steps in initiating the autophagy pathway and in this way regulated mitophagy, a specialize autophagy-like process involved in breaking down damaged mitochondria (Joo, Dorsey et al. 2011). Cdc37-fostered autophagy may be important in neurodegenerative diseases such as Amyotrophic Lateral Sclerosis and Alzheimer disease, that are components of the aging process and chaperone complexes may be involved in clearance of misfolded proteins through the autophagy pathway (Jinwal, Abisambra et al. 2012).

Conclusions

Thus Cdc37, as a major component of the protein complex that controls the folding of protein kinases in the cell stands at the hub of a multitude of intracellular signaling networks (Caplan, Ma'ayan et al. 2007, Karnitz and Felts 2007, Gray, Prince et al. 2008). Its effects thus reach beyond the housekeeping pathways of protein folding into a wide range of cellular processes. Further developments may await more information as to the exact role of Cdc37 in molecular chaperone function.

Due to its influence in cell growth pathways Cdc37 has attracted much attention as a potential intermediate in carcinogenesis and indeed proof of concept studies in cell lines indicate that Cdc37 is required for cancer cell signaling and that quenching the influence of the co-chaperone prevents malignant cell growth (Gray, Prince et al. 2008). Cdc37 might be an attractive potential target in cancer due to (1) the fact that it may be expressed to high level in some types of cancer and (2) controls multiple signaling pathways. This indicates a potential for: (1) selectivity due to its elevated expression and (2) robustness as the co-chaperone may control multiple growth signaling pathways and may thus be less prone to evolution of resistance than for other oncoproteins. Currently specific agents to target Cdc37 are not available.

Protein aggregation disorders have been linked to molecular chaperones and to age related declines in molecular chaperones and co-chaperones (Calderwood, Murshid et al. 2009). Cdc37 appears to be a potential agent in longevity due to its links to protein folding and autophagy and it will be informative to study the role of Cdc37 maintenance / decline in aging organisms. The development of agents that might increase Cdc37 levels may thus be called for to remedy aging relate shortfalls.

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References

Bitting RL and Armstrong AJ (2013). "Targeting the PI3K/Akt/mTOR pathway in castration-resistant prostate cancer." Endocr Relat Cancer 20(3):R83–99. [PubMed: 23456430]

Boellmann F, Guettouche T, Guo Y, Fenna M, Mnayer L and Voellmy R (2004). "DAXX interacts with heat shock factor 1 during stress activation and enhances its transcriptional activity." Proc Natl Acad Sci U S A 101(12): 4100–4105. [PubMed: 15016915]

Calderwood SK (2013). "Molecular cochaperones: tumor growth and cancer treatment." Scientifica (Cairo) 2013: 217513. [PubMed: 24278769]

Calderwood SK and Gong J (2012). "Molecular chaperones in mammary cancer growth and breast tumor therapy." J Cell Biochem 113(4): 1096–1103. [PubMed: 22105880]

Calderwood SK, Khaleque MA, Sawyer DB and Ciocca DR (2006). "Heat shock proteins in cancer: chaperones of tumorigenesis." Trends Biochem Sci 31(3): 164–172. [PubMed: 16483782]

Calderwood SK, Murshid A and Prince T (2009). "The shock of aging: molecular chaperones and the heat shock response in longevity and aging--a mini-review." Gerontology 55(5): 550–558. [PubMed: 19546513]

Caplan AJ, Ma'ayan A and Willis IM (2007). "Multiple kinases and system robustness: a link between Cdc37 and genome integrity." Cell Cycle 6(24): 3145–3147. [PubMed: 18075309]

Caplan AJ, Mandal AK and Theodoraki MA (2007). “Molecular chaperones and protein kinase quality control.” Trends Cell Biol 17(2): 87–92. [PubMed: 17184992]

Ciocca DR, Arrigo AP and Calderwood SK (2013). “Heat shock proteins and heat shock factor 1 in carcinogenesis and tumor development: an update.” Arch Toxicol 87(1): 19–48. [PubMed: 22885793]

Ciocca DR and Calderwood SK (2005). “Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications.” Cell Stress Chaperones 10(2): 86–103. [PubMed: 16038406]

Cox MB and Johnson JL (2011). “The role of p23, Hop, immunophilins, and other co-chaperones in regulating Hsp90 function.” Methods Mol Biol 787: 45–66. [PubMed: 21898226]

Dey B, Lightbody JJ and Boschelli F (1996). “CDC37 is required for p60v-src activity in yeast.” Mol Biol Cell 7(9): 1405–1417. [PubMed: 8885235]

Ellis RJ (2007). “Protein misassembly: macromolecular crowding and molecular chaperones.” Adv Exp Med Biol 594: 1–13. [PubMed: 17205670]

Fliss AE, Fang Y, Boschelli F and Caplan AJ (1997). “Differential in vivo regulation of steroid hormone receptor activation by Cdc37p.” Mol Biol Cell 8(12): 2501–2509. [PubMed: 9398671]

Gray PJ Jr., Prince T, Cheng J, Stevenson MA and Calderwood SK (2008). “Targeting the oncogene and kinome chaperone CDC37.” Nat Rev Cancer 8(7): 491–495. [PubMed: 18511936]

Gray PJ Jr., Stevenson MA and Calderwood SK (2007). “Targeting Cdc37 inhibits multiple signaling pathways and induces growth arrest in prostate cancer cells.” Cancer Res 67(24): 11942–11950 [PubMed: 18089825]

Heinlein CA and Chang C (2004). “Androgen receptor in prostate cancer.” Endocr Rev 25(2): 276–308. [PubMed: 15082523]

Jinwal UK, Abisambra JF, Zhang J, Dharia S, O’Leary JC, Patel T, Braswell K, Jani T, Gestwicki JE and Dickey CA (2012). “Cdc37/Hsp90 protein complex disruption triggers an autophagic clearance cascade for TDP-43 protein.” J Biol Chem 287(29): 24814–24820. [PubMed: 22674575]

Joo JH, Dorsey FC, Joshi A, Hennessy-Walters KM, Rose KL, McCastlain K, Zhang J, Iyengar R, Jung CH, Suen DF, Steeves MA, Yang CY, Prater SM, Kim DH, Thompson CB, Youle RJ, Ney PA, Cleveland JL and Kundu M (2011). “Hsp90-Cdc37 chaperone complex regulates Ulk1- and Atg13-mediated mitophagy.” Mol Cell 43(4): 572–585. [PubMed: 21855797]

Karnitz LM and Felts SJ (2007). “Cdc37 regulation of the kinome: when to hold ‘em and when to fold ‘em.” Sci STKE 2007(385): pe22. [PubMed: 17488976]

Lavictoire SJ, Parolin DA, Klimowicz AC, Kelly JF and Lorimer IA (2003). “Interaction of Hsp90 with the nascent form of the mutant epidermal growth factor receptor EGFRvIII.” J Biol Chem 278(7): 5292–5299. [PubMed: 12471035]

MacLean M and Picard D (2003). “Cdc37 goes beyond Hsp90 and kinases.” Cell Stress Chaperones 8(2): 114–119. [PubMed: 14627196]

Miyata Y and Nishida E (2005). “CK2 binds, phosphorylates, and regulates its pivotal substrate Cdc37, an Hsp90-cochaperone.” Mol Cell Biochem 274(1–2): 171–179. [PubMed: 16335536]

Mollapour M, Tsutsumi S, Truman AW, Xu W, Vaughan CK, Beebe K, Konstantinova A, Vourganti S, Panaretou B, Piper PW, Trepel JB, Prodromou C, Pearl LH and Neckers L (2011). “Threonine 22 phosphorylation attenuates Hsp90 interaction with cochaperones and affects its chaperone activity.” Mol Cell 41(6): 672–681. [PubMed: 21419342]

Pearl LH (2005). “Hsp90 and Cdc37 -- a chaperone cancer conspiracy.” Curr Opin Genet Dev 15(1): 55–61. [PubMed: 15661534]

Perdew GH, Wiegand H, Vanden Heuvel JP, Mitchell C and Singh SS (1997). “A 50 kilodalton protein associated with raf and pp60(v-src) protein kinases is a mammalian homolog of the cell cycle control protein cdc37.” Biochemistry 36(12): 3600–3607. [PubMed: 9132011]

Rao J, Lee P, Benzeno S, Cardozo C, Albertus J, Robins DM and Caplan AJ (2001). “Functional interaction of human Cdc37 with the androgen receptor but not with the glucocorticoid receptor.” J Biol Chem 276(8): 5814–5820. [PubMed: 11085988]

Reed SI (1980). “The selection of amber mutations in genes required for completion of start, the controlling event of the cell division cycle of S. cerevisiae.” Genetics 95(3): 579–588. [PubMed: 7002719]

Salminen A, Lehtonen M, Paimela T and Kaarniranta K (2010). "Celastrol: Molecular targets of Thunder God Vine." Biochem Biophys Res Commun 394(3): 439–442. [PubMed: 20226165]

Santagata S, Hu R, Lin NU, Mendillo ML, Collins LC, Hankinson SE, Schnitt SJ, Whitesell L, Tamimi RM, Lindquist S and Ince TA (2011). "High levels of nuclear heat-shock factor 1 (HSF1) are associated with poor prognosis in breast cancer." Proc Natl Acad Sci U S A 108(45): 18378–18383. [PubMed: 22042860]

Smith JR and Workman P (2009). "Targeting CDC37: an alternative, kinase-directed strategy for disruption of oncogenic chaperoning." Cell Cycle 8(3): 362–372. [PubMed: 19177013]

Stepanova L, Finegold M, DeMayo F, Schmidt EV and Harper JW (2000). "The oncoprotein kinase chaperone CDC37 functions as an oncogene in mice and collaborates with both c-myc and cyclin D1 in transformation of multiple tissues." Mol Cell Biol 20(12): 4462–4473. [PubMed: 10825210]

Stepanova L, Yang G, DeMayo F, Wheeler TM, Finegold M, Thompson TC and Harper JW (2000). "Induction of human Cdc37 in prostate cancer correlates with the ability of targeted Cdc37 expression to promote prostatic hyperplasia." Oncogene 19(18): 2186–2193. [PubMed: 10822368]

Summy JM, Sudol M, Eck MJ, Monteiro AN, Gatesman A and Flynn DC (2003). "Specificity in signaling by c-Yes." Front Biosci 8: s185–205. [PubMed: 12456296]

Taipale M, Jarosz DF and Lindquist S (2010). "HSP90 at the hub of protein homeostasis: emerging mechanistic insights." Nat Rev Mol Cell Biol 11(7): 515–528. [PubMed: 20531426]

Taipale M, Krykbaeva I, Koeva M, Kayatekin C, Westover KD, Karras GI and Lindquist S (2012). "Quantitative analysis of HSP90-client interactions reveals principles of substrate recognition." Cell 150(5): 987–1001. [PubMed: 22939624]

Turnbull EL, Martin IV and Fantes PA (2005). "Cdc37 maintains cellular viability in Schizosaccharomyces pombe independently of interactions with heat-shock protein 90." FEBS J 272(16): 4129–4140. [PubMed: 16098195]

Vaughan CK, Gohlke U, Sobott F, Good VM, Ali MM, Prodromou C, Robinson CV, Saibil HR and Pearl LH (2006). "Structure of an Hsp90- Cdc37-Cdk4 complex." Mol Cell 23(5): 697–707. [PubMed: 16949366]

Wu F, Peacock SO, Rao S, Lemmon SK and Burnstein KL (2013). "Novel interaction between the co-chaperone Cdc37 and Rho GTPase exchange factor Vav3 promotes androgen receptor activity and prostate cancer growth." J Biol Chem 288(8): 5463–5474. [PubMed: 23281476]

Xu W, Mollapour M, Prodromou C, Wang S, Scroggins BT, Palchick Z, Beebe K, Siderius M, Lee MJ, Couvillon A, Trepel JB, Miyata Y, Matts R and Neckers L (2012). "Dynamic tyrosine phosphorylation modulates cycling of the HSP90-P50(CDC37)-AHA1 chaperone machine." Mol Cell 47(3): 434–443. [PubMed: 22727666]

Xu W and Neckers L (2012). "The double edge of the HSP90- CDC37 chaperone machinery: opposing determinants of kinase stability and activity." Future Oncol 8(8): 939–942. [PubMed: 22894668]

Zou J, Guo Y, Guettouche T, Smith DF and Voellmy R (1998). "Repression of heat shock transcription factor HSF1 activation by HSP90 (HSP90 complex) that forms a stress-sensitive complex with HSF1." Cell 94(4): 471–480. [PubMed: 9727490]

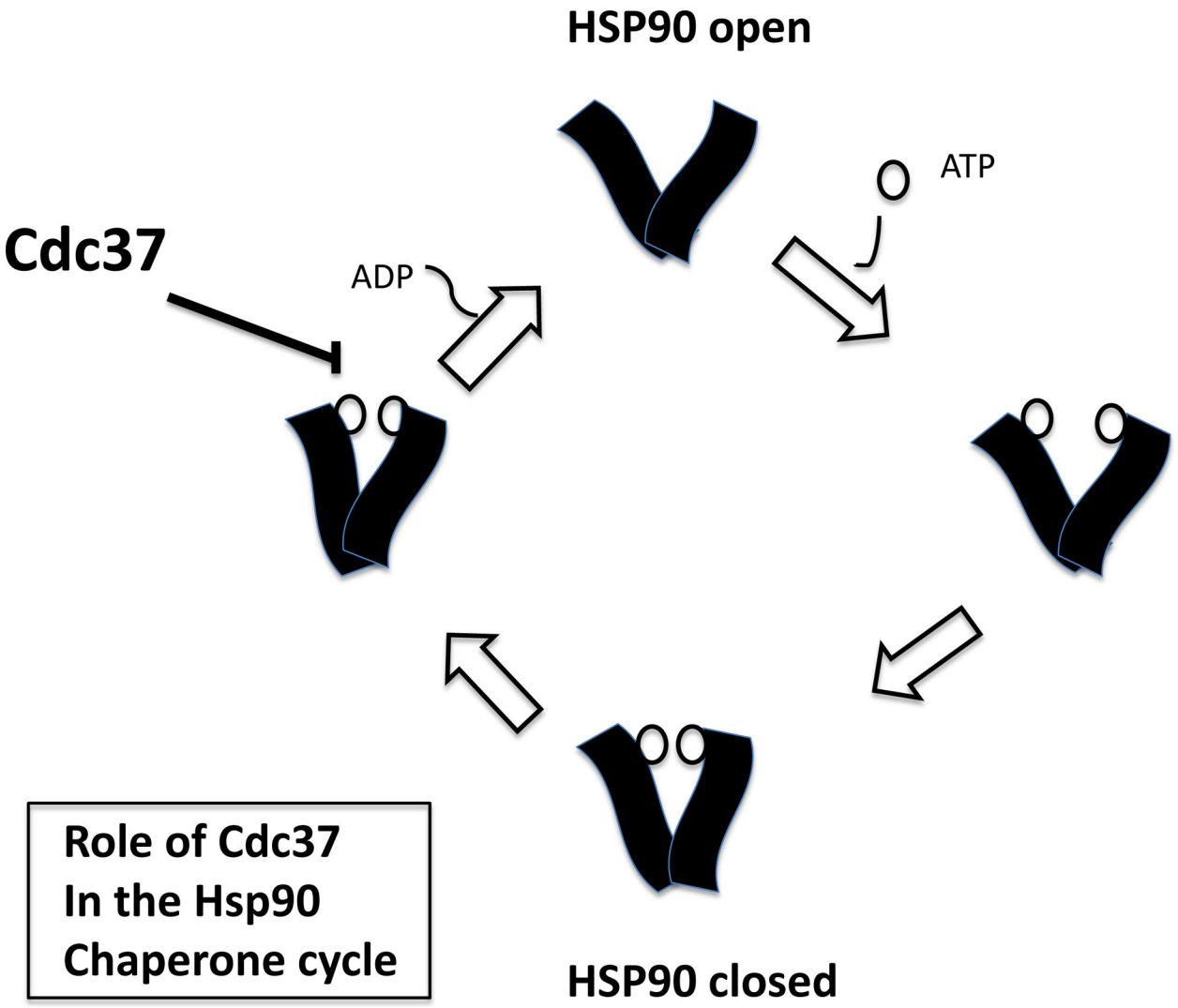

Figure 1. Role of Cdc37 in the Hsp90 chaperone cycle.

The figure depicts the HSP90 dimer going through a cycle of ATP binding and hydrolysis. ATP bound HSP90 is capable of client binding while ATP hydrolysis and ADP dissociation leads to client release. The bound client undergoes folding during this cycle. Cdc37 inhibits the ATP hydrolysis step and permits prolonged association of Hsp90 dimers with client proteins and more effective chaperone activity. In addition to association with Hsp90, Cdc37 also binds the client in a ternary complex (not shown). Client binding to Hsp90 and to Cdc37 both assist in molecular chaperone function.

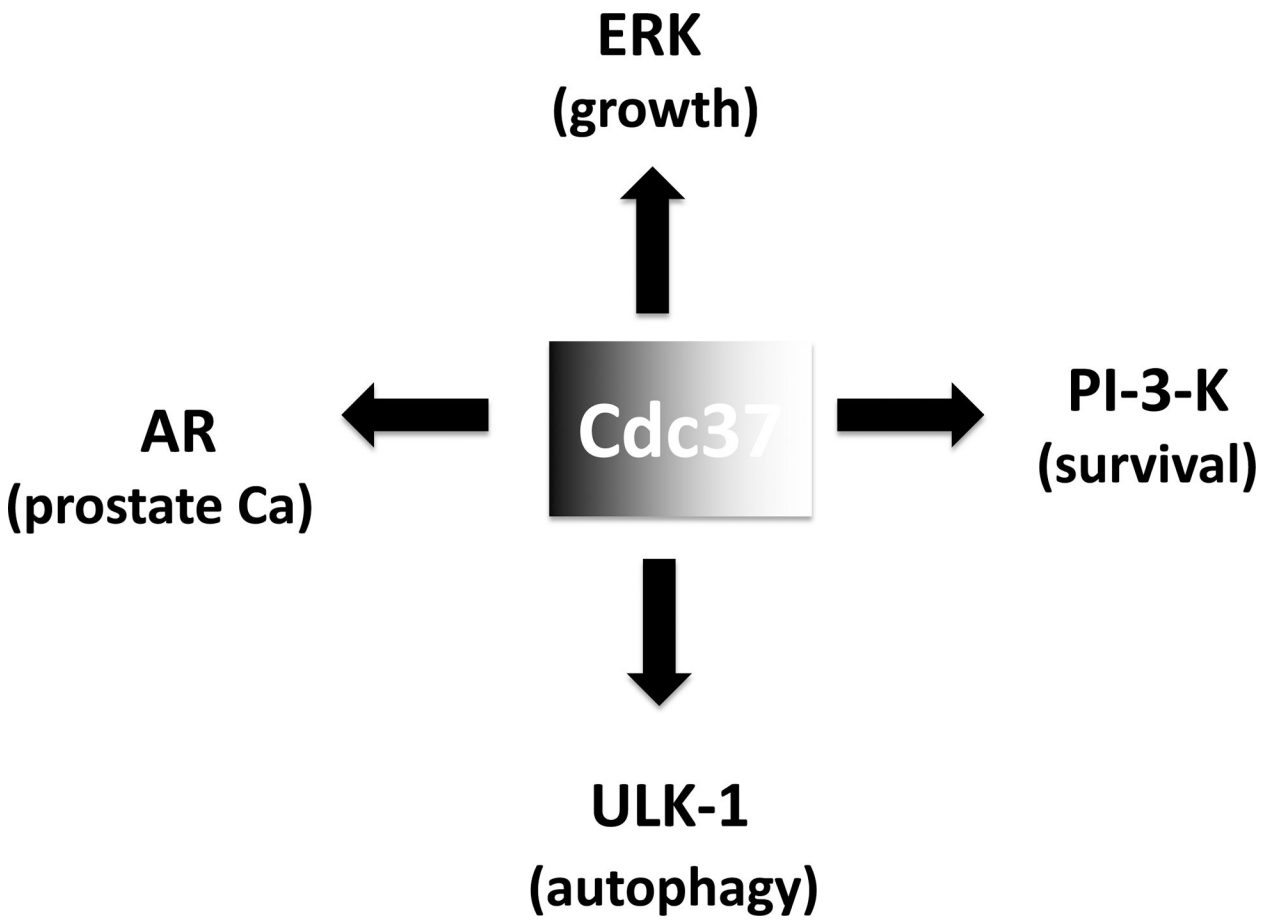

Figure 2. Cdc37 controls a network of intracellular protein kinases.

Cdc37 is able to bind to a wide spectrum of protein kinases through their highly conserved catalytic domain. Depicted here is Cdc37 regulation of the ERK-MAP kinase pathway, the phosphatidylinositol-3-kinase (PI-3-K) pathway, Unc-51-like kinase (ULK-1) activity and the activity of AR. The interactions with ERK and PI-3-K are not direct but involve other members of these cascade reactions. In this way, Cdc37 is able to control a wide spectrum of intracellular metabolic pathways involved in cell growth, survival, autophagy and carcinogenesis. AR seems to be exceptional in being a non-kinase client of Cdc37.