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The oncogene Cdc37 is a molecular chaperone: Targeting The Kinome's Favorite Aunt

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Abstract

Cdc37 is a molecular chaperone that physically stabilizes the catalytic domains found in protein kinases and is therefore a wide-spectrum regulator of protein phosphorylation. It is also an overexpressed oncogene that mediates carcinogenesis by stabilizing the compromised structures of mutant and/or overexpressed oncogenic kinases. Recent work shows that such dependency of malignant cells on elevated Cdc37 expression is a vulnerability that can be targeted in cancer by agents that deplete or inhibit Cdc37. Cdc37 is thus a candidate for broad-spectrum molecular cancer therapy.

Although Cdc37 is overexpressed in a number of cancers, it is an unusual oncoprotein whose transforming character does not readily snap into place in the conventional oncogenic pathways. Instead, it is a molecular chaperone, a protein that facilitates folding/refolding of other proteins, often described as its “clients”. The role of molecular chaperones in cancer was first characterized with regard to Hsp90 (for review see⁵). Hsp90 is a facilitator of oncogenesis that stabilizes a wide range of overexpressed or mutated oncogenic proteins and permits their tumorigenic influence to arise^{3,7}. Tumors thus appear to become *addicted to chaperones* and can be treated by withdrawing the chaperoning power of Hsp90^{4–6}. Cdc37 interacts with a subset of client proteins within Hsp90 complexes and plays a specialized role as primary partner in kinome maintenance^{3,8,9}. This specialized property of Cdc37 fuels the acceleration of cell proliferation observed in cancer by promoting the activities of a broad array of protein kinases^{1–3}. These include receptor tyrosine kinases such as EGFR and MET, non-receptor tyrosine kinases v-src and Lck, and intracellular serine/threonine kinases Raf-1, Ksr, Akt, IKK, Cdc2, Cdk2 and Cdk4. A comprehensive list of Cdc37 client kinases, including the ones listed above and others can be found at the website of Dr Didier Picard:

<http://www.picard.ch/downloads/Cdc37interactors.pdf>. The degree of dependency of the cancer cell kinome on Cdc37 expression thus appears to be extensive and in a recent yeast screen, at least 90 % of the protein kinases examined required Cdc37 for function¹⁰.

The defining cellular role for Cdc37, which becomes misappropriated in cancer, resides in its promotion of cell proliferation. Indeed this protein was first discovered in a yeast screen for cell division cycle proteins, hence its name¹¹. Thus when mammalian tissues undergo rapid proliferation during development, the normally scarce levels of Cdc37 are rapidly expanded. Elevated levels of Hsp90/Cdc37 complexes mediate the maturation and stabilization of protein

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Because of space limitations we were unable to cite many significant studies on Cdc37 and Hsp90. We apologize to the authors of such studies and refer to excellent publications that cite the literature more inclusively.^{1–6}

kinases required for proliferation or perhaps for repeated rounds of kinase re-activation^{9,12,13}. For instance, increased levels of Cdc37 *in vivo* correlate with the upregulation of the G₁-specific cyclin D1 in proliferating normal tissues³. Cyclin D1 is the partner of Cdk4, a Cdc37-dependent cell cycle kinase. Elevated Cdc37 levels also mediate cancer cell growth, although the degree to which changes in Cdc37 regulation in proliferating normal tissues resemble those in malignant tissues is not clear. The role of Cdk4 as a key Cdc37 client in cancer is compelling, although the much larger cast of oncogenic signaling molecules mentioned above also require Cdc37. Proliferating tumor cells may also have an expanded dependency on Cdc37 due to the increased repertoire of overexpressed/mutated kinases that mediate their growth (in accordance with the *addicted to chaperones* hypothesis)⁵. However, the degree to which Cdc37 responds to the quality or quantity of clients in these contrasting proliferative states is yet to be determined.

The amplified levels of Cdc37 in prostate cancer suggest that it may be of particular significance in this type of neoplasm^{8,14,15}. Indeed, in recent immunohistological studies, Cdc37 overexpression was found in 100% of neoplastic prostate tissue, compared with normal prostate⁸. Although the rationale for this is not certain, one rather compelling suggestion involves the role of Cdc37 in androgen signaling, a key pathway in prostatic cell growth. The androgen receptor (AR) is a rare non-kinase Cdc37 client¹⁶. Although Hsp90 plays a general role in maintaining the function of nuclear receptors, Cdc37 specifically associates with AR in contrast to closely-related nuclear receptors including the glucocorticoid receptor (GR)¹⁶. Cdc37 associates with the ligand-binding domain of AR permitting the structural changes that accompany ligand encounter, factor activation and cell proliferation.

Structural mechanisms of Cdc37-kinase interaction

Strategies for targeting Cdc37 in cancer treatment will be aided by considering the biochemical and ultrastructural nature of the Cdc37-client interaction. The two best known properties of Cdc37 are its abilities to: (1) bind to clients and (2) associate with Hsp90, functions which involve two major structural domains^{2,9,10} (Fig. 1). The kinase binding domain (human, 1–126 aa) is the most highly conserved region among Cdc37 homologs and contains several key residues whose mutation or deletion each alter kinase binding². The residue with most regulatory significance is serine (S) 13 whose phosphorylation permits stable interaction of Cdc37 with client kinases¹⁷. In turn, the kinase which phosphorylates S13, casein kinase II is in itself a Cdc37 client, and mediates a positive feedback loop between the client kinase and Cdc37 chaperoning¹⁸. A second region within Cdc37 (127–282 aa) interacts with the N-terminal ATP-binding domain of Hsp90. This interaction is predicted not only to mediate recruitment of client kinases to Hsp90 but also to regulate the Hsp90 ATPase activity required for chaperone activity². By contrast the C-terminal domain (282–378 aa) of Cdc37 remains relatively uncharacterized. In both *S. cerevisiae* and *S. pombe*, only the amino terminal “client interface” domain is required to support growth, suggesting that Hsp90 is dispensable for the growth-promoting functions of Cdc37^{19,20}. However, in mammalian cells the homologous construct functions as a dominant negative inhibitor of wild type Cdc37 and a growth antagonist in prostate carcinoma cells¹⁵. This of course does not rule out Hsp90 independent actions of Cdc37 but rather suggests a shift in emphasis towards Hsp90-dependent interactions in mammalian cells. Such differences between these classes of eukaryote may reflect the rather meager degree of sequence conservation between the mammalian and yeast molecules, which is less than 20% and make inferences derived from yeast studies somewhat uncertain for prediction of Cdc37 behavior in cancer². Of particular note, the affinity of mammalian Cdc37 for Hsp90 exceeds that of the *S. cerevisiae* homolog by greater than tenfold². Mammalian Cdc37 in tumor cells may thus have an increased tendency to function within a ternary complex containing the client kinase and Hsp90 (Fig. 1), although independent functions for Cdc37 cannot be ruled out.

Protein kinases in all cells become associated with Cdc37 and Hsp90 in a stepwise process based largely on the paradigm first established for GR folding and maturation²¹. Initial kinase folding involves association with the chaperones Hsp70 and Hsp40 followed by a series of ATP-fueled steps that lead to assembly of a folding complex containing Hsp90 and its cohorts including Cdc37 bound to the kinase^{4,5}. The more stable clients then exit the Cdc37-Hsp90 complex, although particularly sensitive kinases bind persistently to the Hsp90 complexes. Such unstable clients proliferate in tumor cell populations due to competition and selection for cells expressing variant and super-abundant mutant kinase variants that mediate tumor progression (2).

Considering the interaction from the viewpoint of the kinase, both Cdc37 and Hsp90 bind directly to the catalytic domain² (Fig. 1). The conserved catalytic domain is comprised of two lobes separated by a deep ATP-binding cleft. Cdc37 associates with the N-terminal lobe while Hsp90 interacts with both lobes^{2,22,23}. The N-lobe is more loosely packed in terms of polypeptide chain folding and can thus comprise a hazard in terms of tendency to unfold, lose function and nucleate degradation cascades^{22,23}. Moreover, each kinase-chaperone interaction shows characteristic properties despite the catalytic domain being the third most common in the human genome²⁴. Indeed, due to subtle differences in N-lobe structure, some kinases may need persistent interactions with Hsp90 and Cdc37 for function and stability². Other kinases may be stabilized by additional intramolecular domains and/or by regulatory partner proteins that bring stability along with substrate specificity²³. For instance Cdk4 binds initially to Hsp90 and Cdc37 until encountering cyclin D1 and forming a Cdk4-Cyclin D1 complex sufficiently stable to be independent of further chaperone interaction²⁵. Other kinases such as the oncogenic *c-erb-B2* bind persistently to chaperone complexes even in the active form (reviewed²). It is predicted that the proliferation of mutation-activated kinases in tumors will lead to a greater dependency on Cdc37 chaperoning. Indeed, individual kinase targets may undergo continuous evolution in terms of Cdc37 dependency due to the emergence of novel mutant forms. Future approaches to individualized care may involve screening for the emergence of Cdc37 dependent kinase mutants. Drugs that inhibit the ATPase activity of Hsp90 further destabilize these quasi-stable clients⁵. This concept has been reaffirmed in studies with anti-cancer drugs that bind and stabilize the ATP binding groove of client kinases and are able to prevent their proteasomal degradation via Hsp90 inhibition. Indeed, the exchange of ATP in activated kinases induces their destabilization and interaction with Cdc37 and Hsp90. Thus mutations that allow a kinase to develop “fast” activity also result in the kinase becoming structurally “loose,” with Cdc37 and Hsp90 helping maintain this “fast and loose” existence. Hsp90 inhibitors are currently undergoing clinical trial⁴. Understanding the dynamics of kinase-Cdc37-Hsp90 interaction may be of particular significance for prediction of kinases in cancer cells most adversely affected by Hsp90 and/or Cdc37 inhibition and facilitation of anti-Cdc37 drug design. (For a definitive review of Cdc37 and protein kinase interactions see:²).

Targeting Cdc37 in cancer

As mentioned earlier, Cdc37 is an overexpressed oncogene. Indeed, under forced *Cdc37* expression cells become transformed, proliferate and tumors arise. When Cdc37 is overexpressed along with the proto-oncogene *c-Myc*, the effects of both agents become amplified and more and larger tumors arise in transgenic mice^{15,8,14}. Indeed, Cdc37 levels are elevated in many clinical cancers⁸. Although Cdc37 may be regarded as a specialized partner of Hsp90, dealing with structurally compromised kinase clients, it may also offer a preferable target for cancer therapy. Hsp90 is expressed with similar abundance in normal and malignant cells and includes among its clientele proteins required for the viability of normal cells²⁶. In its favor as a therapeutic target, some studies indicate that tumor Hsp90 is selectively vulnerable due to the proliferation of its oncogenic clients and the formation of mature Hsp90/client/co-chaperone complexes that bind Hsp90 drugs with increased affinity²⁷. However this

phenomenon is not universally observed²⁸. Cdc37, by contrast is increased in proliferating tissues, and is heavily expressed in certain cancers including prostate carcinoma, anaplastic large cell lymphoma, acute myelocytic leukemia, hepatocellular carcinoma and multiple myeloma^{29–32}. As most normal tissues do not proliferate or appear to require Cdc37, a potential therapeutic window is available, which is not as obvious in the case of Hsp90.

The mechanisms underlying increased Cdc37 expression in malignant cells are not known. The Cdc37 promoter contains multiple binding sites for transcription factor Mzf1, implicated in myeloid tumorigenesis, although evidence for a dynamic role in Cdc37 expression is not available³³. The *addicted to chaperones* hypothesis might predict that chaperone levels should increase as clients proliferate. Indeed, there is a clear rationale for this mechanism in the case of Hsp90 whose transcription is activated by the factor HSF1 which undergoes induction by increased accumulation of unfolded proteins³⁴. However, the Cdc37 promoter is devoid of canonical HSF1 binding elements and does not respond to HSF1 activation. A further clue that warrants exploration is that Cdc37 is overexpressed in prostate cancer and such cancers are induced by the forced expression of Cdc37^{8,14}. As AR is one of the rare non-kinase clients for Cdc37, and is essential for proliferation and differentiation of prostatic epithelium, a role for AR would fit the profile⁸.

Recent studies address the feasibility of targeting Cdc37 in prostate carcinoma^{15,35}. Indeed, depletion of Cdc37 in prostate cancer cell lines by RNA interference techniques leads to permanent growth inhibition both in androgen-dependent and androgen-independent cell lines³⁵. Growth inhibition was correlated with decreased signaling through the anabolic ERK and Akt kinase cascades as well as reduced AR-dependent transcriptional signaling³⁵ (Fig 2). In addition, Cdc37 targeting inhibits HSF1 activity and Hsp70 expression, components of a common resistance pathway that mediates insensitivity to therapeutics such as Hsp90 inhibitors and proteasomal targeting agents^{35,36} (Fig 2). Inactivation of Cdc37 may thus decrease cell survival through a range of pathways, permitting effective inhibition of anabolic signaling and breaking resistance to cytotoxic therapy. It is significant that the consequences of Cdc37 depletion and Hsp90 inhibition are divergent at the molecular level, with Hsp90 inactivation triggering degradation of the abandoned clients while Cdc37 depletion does not³⁵ (Fig 3). Cdc37 knockdown instead causes profound inhibition of the activities of multiple kinase cascades and loss of the transcriptional activity of AR³⁵. These data suggest intrinsic differences in the relationships between Hsp90, Cdc37 and their clients that become unmasked during therapy. Cdc37 is evidently not essential for the intracellular survival of its clients while functional Hsp90 is required to prevent degradation³⁷ (Fig 3). However, in order for protein kinases to transfer phosphate to their substrates or for AR to interact productively with its ligand, Cdc37 is indispensable. Further underlining the contrasting mechanisms of Hsp90- and Cdc37-dependent prostate cancer growth, functional inhibition of both proteins in tumor cells is supra-additive³⁵. The question of independent, non-Hsp90 requiring interactions for Cdc37 observed in recent studies also arises²⁰.

Recent work also shows that depletion of another Hsp90 co-chaperone AHA1 leads to a similar reduction in activity of Hsp90 client kinases without marked increases in degradation of such proteins. These findings suggest that degradation of clients may require direct interaction between drugged, inactive Hsp90 and its bound clients and cannot be mimicked by the inactivation of co-chaperones³⁸. Targeting Hsp90 co-chaperones may therefore lead to radically different consequences compared to the direct inhibition of Hsp90. Future strategies for Cdc37 drug design and selection would likely aim at the inhibition of either: (1) the Cdc37-client interaction or (2) Cdc37-Hsp90 association (Fig 1). Indeed recent studies using the triterpine drug celastrol indicate cancer cell growth reduction through mechanism (2) the inhibition of Hsp90-Cdc37 interaction³⁹. These natural plant products cause pleiotropic changes in cancer cells and can lead to tumor regression³⁹. However, the cellular responses to

celastrol resemble those provoked by Hsp90 inhibitors, and include client protein destruction and HSF1 activation and may not provide a radical departure from current treatments. Further studies might concentrate on agents with more novel mechanisms of action such as Cdc37-client interaction.

In conclusion, inhibition of Cdc37 activity is a promising new approach to the treatment of cancer due to its multi-targeting nature, the elevated expression of Cdc37 in dividing cells and the ability of Cdc37 depletion to arrest growth in both AR+ and AR- prostate cancer. Cdc37 targeting also has the potential ability to deter the evolution of new traits that depend on kinase mutation and such a block on adaptation might limit the ability of tumors to respond to therapy and a deteriorating microenvironment. Such effects are proposed to occur in tumors treated with Hsp90-targeting drugs⁵. As to the ultimate selectivity of Cdc37 inhibition for treating malignant cells, this chaperone is not expressed in quiescent cells but appears necessary for the growth of normal epithelial cells. Therefore treating prostate cancer through the inhibition of Cdc37 might involve sacrificing this non-essential population¹⁵. However, this drawback would not differ markedly from current therapies used to treat prostate cancer, which also focus on eradicating normal prostate tissue as well as cancer. One potential concern with this therapy could however be the unknown potential for effects on other normally proliferating epithelium including that in the GI tract and skin.

Future Directions

More remains to be learned regarding the oncogenic role of Cdc37 and its utility as a target for cancer therapy. Thus we remain uncertain of the full extent of types and stages of cancer mediated by Cdc37 overexpression and such a gap in knowledge will hopefully be rectified in subsequent studies. Future studies will also ask- by which molecular mechanism(s) does Cdc37 become overexpressed during tumor progression? Promising approaches to Cdc37 targeting of malignant tissues that will likely be explored include pharmacological disruption of Cdc37-client interactions and modulation of phosphorylation of the key residue Serine 13 within the client interaction domain of Cdc37.

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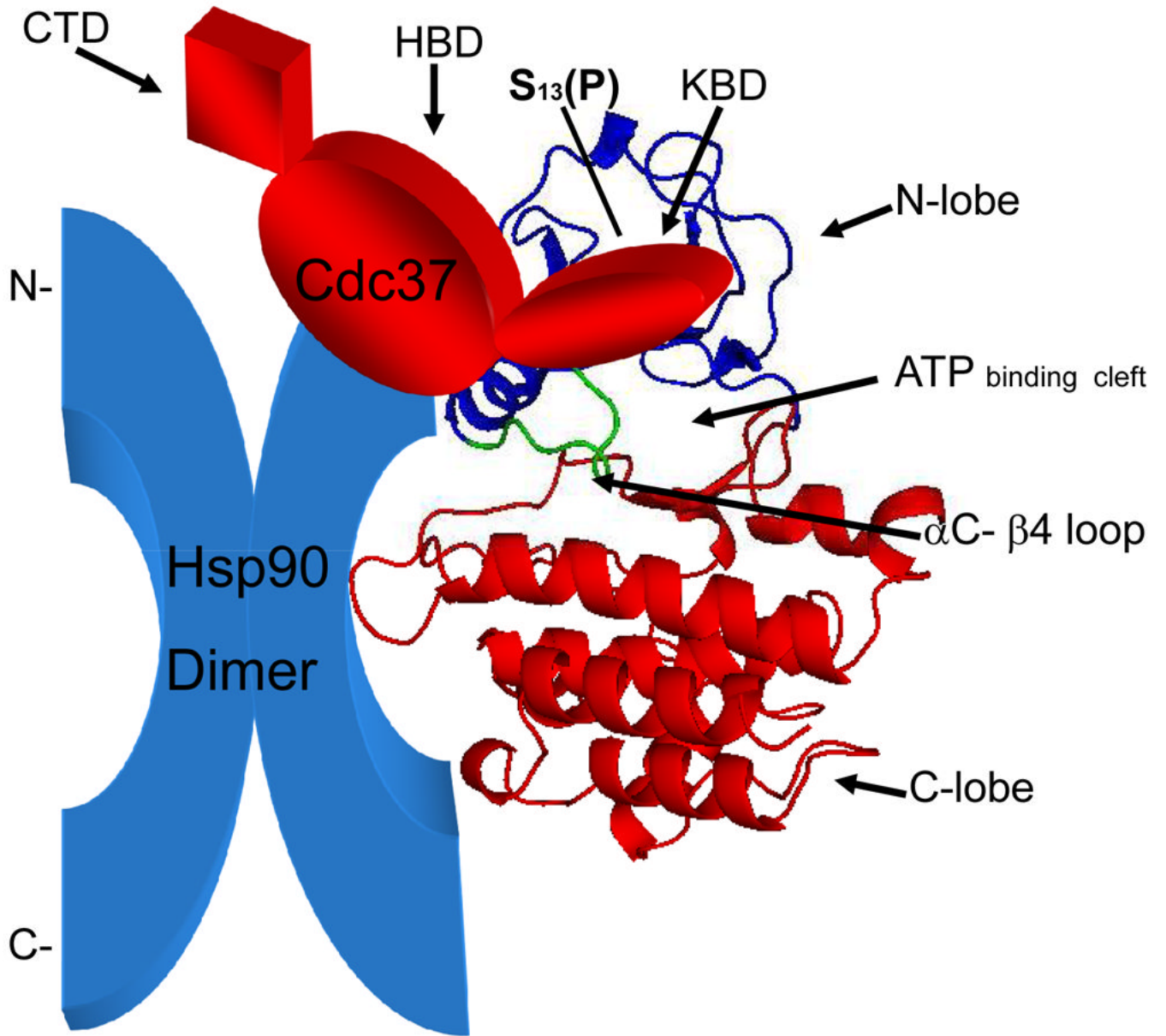


Figure 1. Interaction domains in Cdc37
 The Cdc37 gene contains three major domains including: an N-terminal client kinase interaction domain (KDB) containing the key phosphoresidue S₁₃, a central domain required for Hsp90 binding (HDB) and a C-terminal domain of unknown function (CTD). The catalytic domains of protein kinases depicted in the ribbon diagram contain N (blue) and C (red) lobes. The KDB of Cdc37 (red) binds to the N lobe while Hsp90 (blue) binds to both N and C lobes while interacting with the HDB of Cdc37.

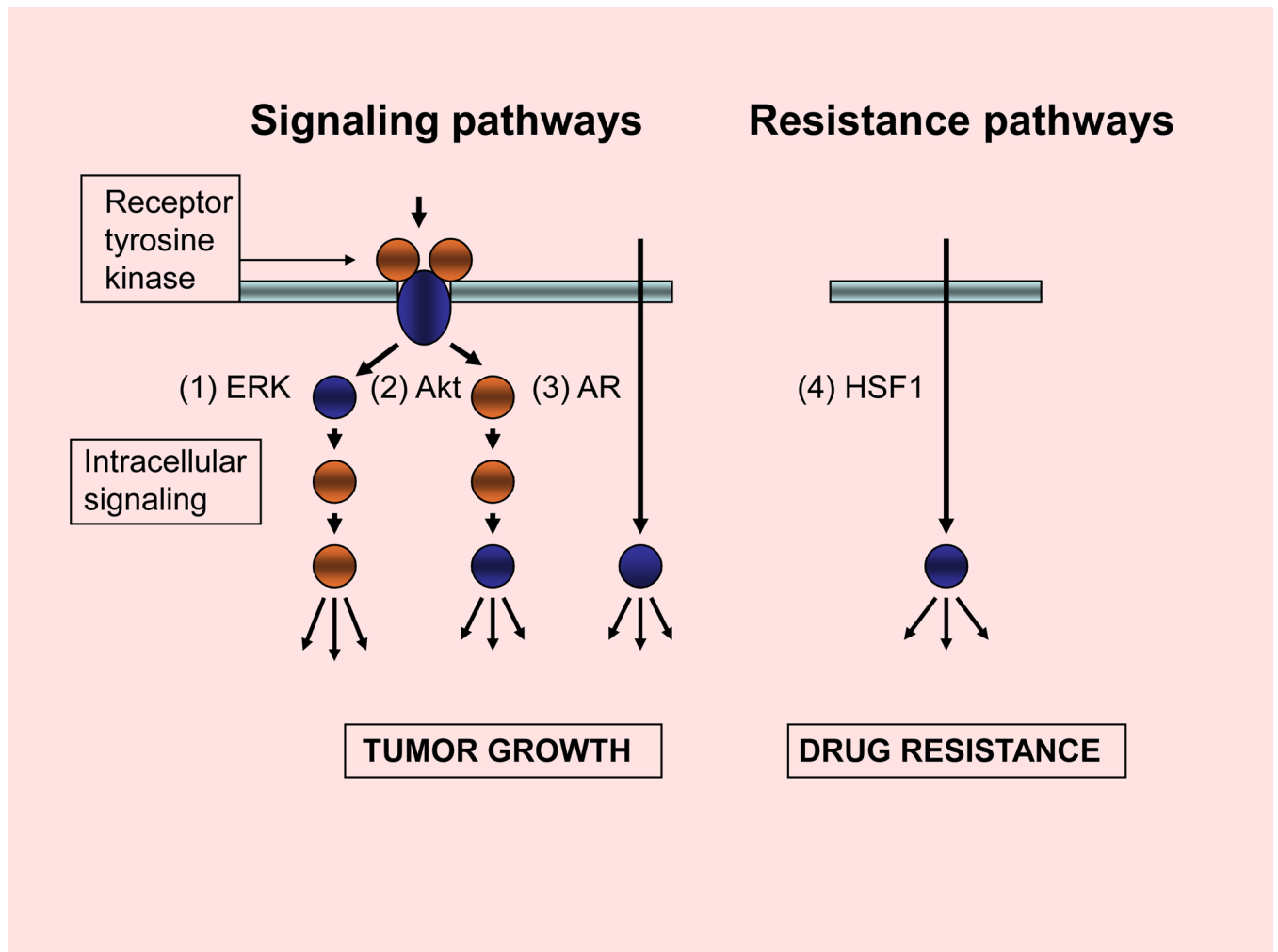


Figure 2. Effects of Cdc37 depletion on anabolic signaling and cell stress pathways
 Cdc37 depletion inhibits signal flux through at least three pathways in prostate carcinoma. These include the (1) ERK, (2) Akt and (3) AR pathways. Depletion of Cdc37 also inhibits (4) the HSF1-mediated heat shock stress response that can be activated by many anti-cancer agents. Well-characterized molecular clients for Cdc37 are indicated by blue coloration.

Contrasting effects of targeting Hsp90 and Cdc37

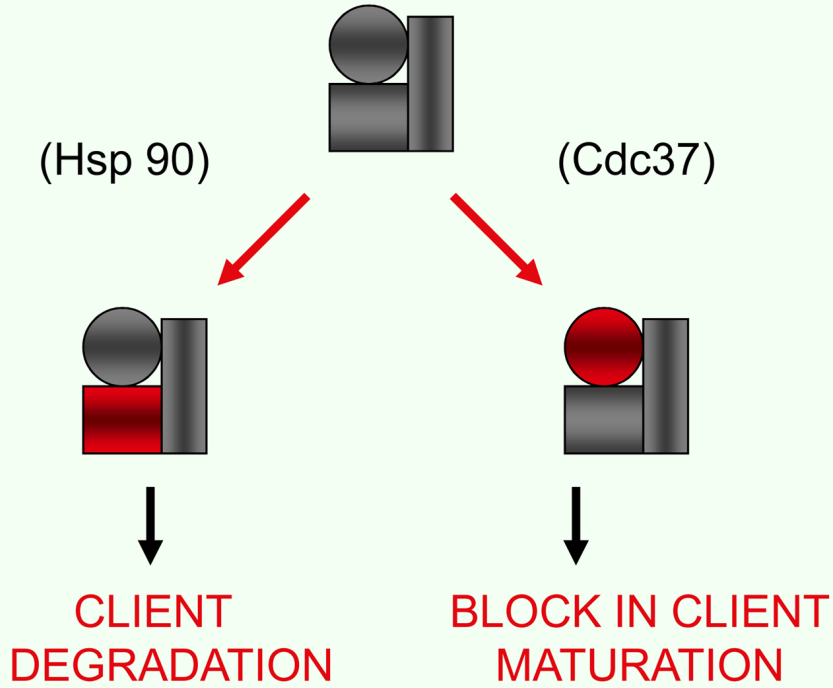


Figure 3. Contrasting effects of targeting Hsp90 and Cdc37
Kinases (≡) interact with both Hsp90 (□) and Cdc37 (○). However, while pharmacological inhibition of Hsp90 (red rectangle) leads to client degradation, depletion of Cdc37 (red circle) causes a block to client maturation and activity that does not involve such extensive client destruction.