The Biology Behind

Targeting the Molecular Chaperone Heat Shock Protein 90 Provides a Multifaceted Effect on Diverse Cell Signaling Pathways of Cancer Cells

□□ *Commentary on Bagatell et al., p.1783, Ramanathan et al., p.1769, Solit et al., p.1775 and Weigel et al., p.1789*

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Heat shock protein 90 (Hsp90) is a molecular chaperone required for the stability and function of several conditionally activated and/or expressed signaling proteins as well as multiple mutated, chimeric, and/or overexpressed signaling proteins, which promote cancer cell growth and/or survival (see the Web site[1] maintained by D. Picard for an up-to-date list). By interacting specifically with a single molecular target, Hsp90 inhibitors cause the eventual inactivation, destabilization, and degradation of numerous chaperone-dependent client proteins, and these drugs have shown promising antitumor activity in preclinical model systems. Several Hsp90 inhibitors, including the benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamycin, are currently undergoing clinical evaluation. The results of four phase I single-agent studies of 17-allylamino-17-demethoxygeldanamycin, two pediatric and two adult trials, are included in this issue of *Clinical Cancer Research* (1–4). Considered as a group, these studies highlight both the promise and the difficulty of successfully developing such molecularly targeted agents for the clinic.

Hsp90 inhibitors are unique in that, although they are directed toward a specific molecular target, they simultaneously inhibit multiple signaling pathways that frequently interact to promote cancer cell survival. The interested reader is referred to several excellent reviews that provide an in-depth description of the many signaling nodes regulated by Hsp90 (5–11). Further, by inhibiting nodal points in multiple overlapping survival pathways used by cancer cells, combination of Hsp90 inhibitors with other chemotherapeutic agents may dramatically increase *in vivo* efficacy. Hsp90 inhibitors have the potential to circumvent the genetic plasticity that allows cancer cells to eventually evade the cytotoxic effects of most molecularly targeted agents.

Hanahan and Weinberg (12) have suggested that the transformation of a normal cell into a cancer cell requires the acquisition of several essential alterations in cell physiology, including self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Because many Hsp90 client proteins play significant roles in each of these alterations, the therapeutic potential of targeting Hsp90 may be best appreciated by considering the possibility of simultaneously targeting the six hallmarks of a cancer cell (Fig. 1).

Targeting Hsp90 to Deprive Cancer Cells of Self-sufficiency in Growth Signals

Environmental growth signals that drive proliferation of a cell are relayed via transmembrane receptors, which often are tyrosine kinases. Many of these are Hsp90 clients. Increased activity of these kinases, because of overexpression or activating mutations, is strongly correlated with cancer progression.

The cell surface tyrosine kinase ErbB2 has a confirmed role in tumorigenesis. In animal models, overexpression of ErbB2 in specific tissues causes cancers to develop in those tissues (13). In patients, ErbB2 is overexpressed in ~30% of breast and prostate cancers, and its overexpression has been associated with a poor clinical prognosis (14). The stability of the ErbB2 protein is inherently dependent on Hsp90, and inhibition of Hsp90 causes a dramatic decrease in ErbB2 protein level, both in cultured cells and in animal tumor models (15, 16). We have also observed, after pharmacologic inhibition of Hsp90, a dramatic decrease in the phosphorylation of ErbB2 as well as of its downstream effectors, suggesting that the intrinsic kinase activity of EbB2 also depends on normal Hsp90 function. Thus, Hsp90 inhibitors are expected to be effective for the treatment of cancers driven by ErbB2 because of either its overexpression or its activating somatic mutation (17, 18).

Recently, investigators have reported that the gefitinib/erlotinib-sensitizing mutation of the epidermal growth factor receptor (EGFR), found in a subset of non–small cell lung cancer patients, confers sensitivity to Hsp90 inhibitors (19), although the mature form of the wild-type EGFR is relatively refractory to these drugs (20). Moreover, mutant EGFRs that develop resistance (or are inherently resistant) to EGFR inhibitors remain sensitive to 17-allylamino-17-demethoxygeldanamycin–induced degradation. Therefore, Hsp90 inhibition should be explored as a potentially fruitful therapeutic strategy for patients whose tumors harbor mutant EGFRs.

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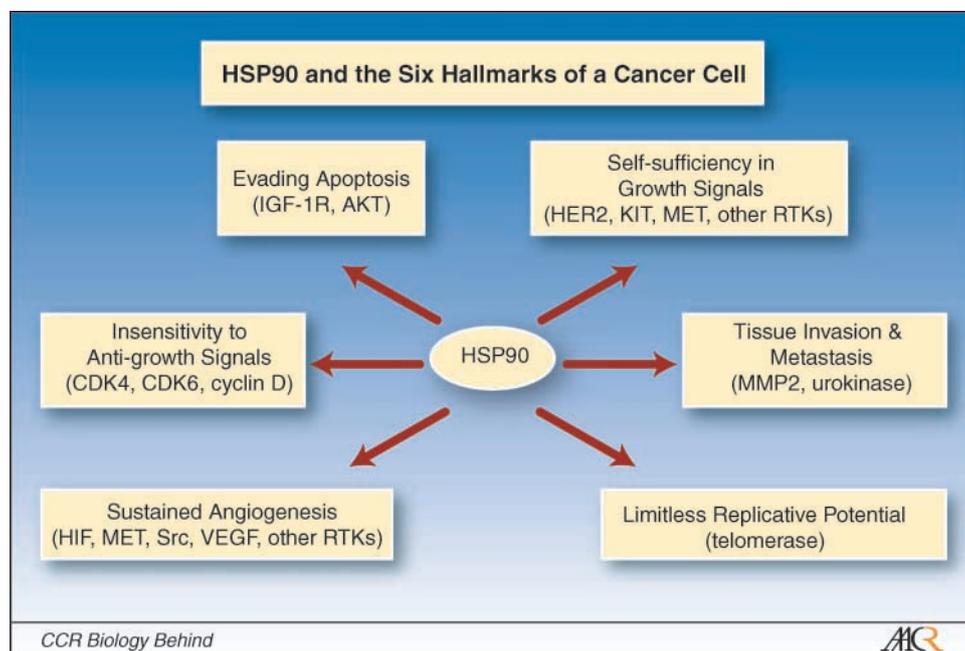[1] http://www.picard.ch/DP/downloads/Hsp90interactors.pdf

Fig. 1. Hsp90 and the six hallmarks of a cancer cell. Multiple Hsp90 client proteins mediate acquisition and maintenance of the six properties necessary for transformation of a normal cell into a cancer cell: (*a*) ability to evade apoptosis, (*b*) ability to be self-sufficient for growth, (*c*) ability to invade surrounding tissue and to metastasize to distant sites, (*d*) ability to undergo limitless replication, (*e*) ability to promote neoangiogenesis, and (*f*) ability to not respond to antigrowth signals. IGF-1R, IGF-I receptor; HIF, hypoxia-inducible factor; RTK, receptor tyrosine kinase; MMP2, matrix metalloproteinase-2. Reprinted from Hanahan and Weinberg (12) ©2000, with permission from Elsevier.

Targeting Hsp90 to Combat Insensitivity of Cancer Cells to Antigrowth Signals

Antiproliferative signals maintain cellular quiescence and tissue homeostasis. These signaling pathways eventually converge on the retinoblastoma protein and retinoblastoma-related proteins, which govern cell transit through the G_1 phase of the cell division cycle. Hypophosphorylated retinoblastoma blocks proliferation by sequestering and altering the function of E2F transcription factors, which in turn control the expression of a wide variety of genes essential for progression from G_1 to S phase. When phosphorylated by activated cyclin-dependent kinase 4 (CDK4), retinoblastoma protein is inactivated and its inhibition of E2F is relaxed, enabling the cell to traverse the cell cycle (21). Thus, deregulation of CDK4, such as caused by inactivating mutation of *INK4B*, bestows resistance to antigrowth signals (22).

CDK4 is a client protein of Hsp90, and Hsp90 inhibitors induce degradation of CDK4 (23). Besides affecting CDK4 proteins directly, Hsp90 inhibitors also reduce expression of cyclin D, which forms an activating complex with CDK4 (24). Together, these effects result in decreased CDK4 expression and activity. Moreover, CDK2, whose activation drives DNA replication and S-G_2 transition, and CDK7, the CDK-activating kinase, are also Hsp90 client proteins (25). Hence, inhibition of Hsp90 function is expected not only to block cancer cells from entering the cell cycle but also to block their progress through that cycle.

Targeting Hsp90 to Induce Apoptosis

Apoptosis is a major means of controlling unwanted expansion of cell populations. Resistance to apoptosis is a hallmark of most and perhaps all types of cancers. Apoptosis can be inhibited by the activation of prosurvival signaling pathways, such as insulin-like growth factor (IGF)-I and its Hsp90-dependent receptor (IGF-I receptor; ref. 26). Activation of this pathway increases the expression of prosurvival factors, such as Bcl-2 and Bcl-xL, while, at the same time, decreasing expression of proapoptotic factors, such as Bim (27). Furthermore, IGF-I receptor activation induces the phosphorylation of Bad. Phosphorylated Bad dissociates from Bcl-xL, liberating its antiapoptotic activity. IGF-I receptor activation also suppresses the activity of caspases, proteases that execute the apoptotic cascade, by inducing their inhibitory phosphorylation as well as expression of caspase inhibitors. Thus, Hsp90 inhibitor-dependent degradation of IGF-I receptor promotes apoptosis in cancer cells that depend on this signaling pathway (26).

Similarly, vascular endothelial growth factor (VEGF) has been reported to induce elevated Bcl-2 protein levels and to inhibit the activity of the proapoptotic caspase-activating protein Apaf in normal endothelial cells and in leukemia cells bearing receptors for VEGF (28). Both phenomena require VEGF-stimulated Hsp90 association with both Bcl-2 and Apaf, and Hsp90 inhibitors have been shown to reverse both of these processes. Thus, Hsp90 inhibition blocks the prosurvival effects of VEGF by preventing both the accumulation of antiapoptotic Bcl-2 and the inhibition of proapoptotic Apaf.

The phosphatidylinositol 3-kinase-Akt pathway is an additional major regulator of apoptosis. In fact, many prosurvival extracellular factors, including EGF and IGF, activate Akt kinase through phosphatidylinositol 3-kinase and 3-phosphoinositide-dependent kinase-1 kinase. Activated Akt induces prosurvival transcription factors, such as nuclear factor-κB, and

suppresses proapoptotic factors, such as the forkhead family of transcription factors. Akt also promotes survival by phosphorylating and inactivating the proapoptotic factor Bad (29). Both Akt and its activating kinase 3-phosphoinositide-dependent kinase-1 are Hsp90 client proteins, and inhibition of Hsp90 induces their degradation (30, 31). Further, in certain contexts, such as overexpression of ErbB2, Hsp90 inhibition also results in rapid Akt dephosphorylation and inactivation (24, 32). Therefore, Hsp90 inhibition deprives cancer cells of multiple survival signals.

Targeting Hsp90 to Ablate Limitless Replicative Potential

Continuous multiplication of mammalian cells is self-limited by an intrinsic process of telomere shortening. Telomeres are noncoding regions at the ends of chromosomes that contain several thousand short repeat sequences. During each replication cycle, chromosomes normally lose 50 to 100 bp in this region because DNA polymerase is unable to completely replicate the 3′ ends of chromosomal DNA. This progressive telomere shortening eventually affects the integrity of the chromosome ends, leading to end-to-end chromosomal fusions that ultimately result in karyotypic disarray and cell death (33).

Cancer cells evade this fate by up-regulating the enzyme telomerase, a ribonucleoprotein that adds hexanucleotide repeats to the ends of chromosomes (34). It has been shown that 85% to 90% of cancer cells express elevated levels of telomerase (35). Increased telomerase maintains the length of telomeres above the critical threshold that permits unlimited chromosomal replication, thus allowing cancer cells to avoid senescence and to become immortal. Active human telomerase minimally consists of two subunits: a catalytic protein component (hTERT) and a template-containing RNA (hTR). Both the assembly of telomerase and the enzymatic activity of hTERT require the function of Hsp90 (36, 37). Thus, inhibition of Hsp90 significantly decreases telomerase activity, reverses the inhibition of telomere shortening, and limits the replication potential of cancer cells.

Targeting Hsp90 to Combat Sustained Angiogenesis

Blood vessels supply oxygen and nutrients, which are essential for cell function and survival. The diffusion rates of these substances obligate virtually all cells to reside within 100 μm of a capillary blood vessel. Therefore, induction and maintenance of angiogenesis are obligatory for the macroscopic growth of cancer cells. Angiogenic ability is acquired during tumor development via an "angiogenic switch" from vascular quiescence. One way to flip the switch is by up-regulating the proangiogenic factor VEGF. VEGF stimulates angiogenesis by binding to and activating its cell surface receptors, promoting endothelial cell proliferation and migration.

Hsp90 inhibition can abate VEGF signaling in two ways. First, VEGF production by cancer cells requires Hsp90, and Hsp90 inhibitors significantly reduce VEGF secretion (38). This activity is likely caused by a decrease in protein level and activity of the Hsp90-dependent transcription factor hypoxia-inducible factor-1α, which positively regulates VEGF expression (39). In addition, the protein stability of VEGF receptors requires Hsp90 function, and Hsp90 inhibitors induce degradation of all three VEGF receptors (38). Therefore, Hsp90 inhibition blocks the proliferation and differentiation of endothelial cells, consequently inhibiting the neovascularization of expanding tumors.

Targeting Hsp90 to Inhibit Tissue Invasion and Metastasis

Invasion into adjacent tissues and metastasis to distant sites are major features of malignant cancer cells and are the cause of 90% of human cancer deaths (40). Invasion and metastasis are complex processes and require coordinated actions of a large assortment of genes, including many kinases. The Met receptor tyrosine kinase, the receptor for hepatocyte growth factor, promotes cancer cell invasion as well as metastasis. Met overexpression is frequently observed in primary tumors, and activating mutations have been identified in patients with papillary renal carcinomas (41). Both wild-type and mutated Met are Hsp90 clients, and their expression and activity are affected by Hsp90 inhibitors (42). Like Met, focal adhesion kinase is a protein kinase that promotes invasion and metastasis. Hsp90 inhibitors have been shown to induce degradation of focal adhesion kinase protein (43) and to block its extracellular matrix–dependent phosphorylation (44).

Although Hsp90 is an intracellular chaperone, it has recently been found expressed at the cell surface of highly metastatic cancer cells (45). Cell surface Hsp90 is also involved in nerve cell migration during development of the central nervous system, and cerebellar neuron migration is experimentally inhibited by Hsp90 antibody (46). Mechanistically, surface Hsp90 was shown to be involved in cytoskeletal organization, which is necessary for lamellipodia formation.

Similar to its role in the developing nervous system, cell surface Hsp90 is required for cancer cell invasion and metastasis. A recent study has shown its involvement in maturation of the cell surface enzyme matrix metalloproteinase-2 (47). The invasion process includes three stages: adhesion to the extracellular matrix, digestion of the matrix to release cells from the tumor mass, and migration of the tumor cell to remote sites. Matrix metalloproteinase-2 can degrade the matrix, providing cancer cells with access to the vasculature and lymphatic system, allowing tumor dissemination. Matrix metalloproteinase-2 was found to form a complex with cell surface Hsp90, and Hsp90 antibody or cell-impermeable pharmacologic inhibitor impaired matrix metalloproteinase-2 maturation and resulted in decreased matrix metalloproteinase-2 activity. Therefore, Hsp90 inhibition interdicts multiple pro-invasion and prometastasis signaling pathways used by cancer cells.

Conclusion

As molecular cancer therapy advances into the 21st century, many efforts have been focused on identifying and specifically inhibiting molecular targets that play distinct roles in cell signaling pathways. Ongoing preclinical and clinical studies suggest that such a strategy is frequently stymied by the high

mutation rate of cancer cells. It is thus exciting to find that such mutated proteins either retain their sensitivity to Hsp90 inhibition (e.g., Bcr-Abl) or acquire a novel dependence on the chaperone not shared by the wild-type protein (e.g., mutated EGFR; refs. 19, 48, 49). Furthermore, Hsp90 is a uniquely appealing molecular target because its inhibition has a coordinated effect on all of the key physiologic alterations on which cancer cells depend for their growth and survival.

Nonetheless, obtaining full benefit of the therapeutic potential of inhibiting Hsp90 will not be trivial as is highlighted by the four phase I clinical trials of 17-allylamino-17-demethoxygeldanamycin, whose findings are published in this issue. It is encouraging that the drug was similarly well tolerated in both pediatric and adult patients, and although no complete or partial responses (as defined by Response Evaluation Criteria in Solid Tumors criteria) were observed, numerous instances of stable disease were reported. It is apparent that an intermittent dosing schedule is necessary to minimize hepatic toxicity, which has proven to be dose limiting in both pediatric and adult patients. Determining whether hepatotoxicity is caused directly by inhibition of Hsp90 or is secondary to drug metabolism requires clinical testing of nonansamycin Hsp90 inhibitors, several of which are currently in various stages of development. Given their current requirement for intermittent dosing, ansamycin Hsp90 inhibitors (such as 17-allylamino-17-demethoxygeldanamycin and most likely 17-dimethylaminoethylamino-17-demethoxygeldanamycin) may be most useful in combination with other agents, and studies exploring this possibility are currently ongoing. Finally, each of these trials calls into question the relevance of monitoring Hsp70 induction in peripheral blood mononuclear cells as a pharmacodynamic end point that is predictive of antitumor activity *in vivo*. Although it was initially important to document biological activity of these novel agents in humans, and peripheral blood mononuclear cells are a readily obtainable tissue source, the very nature of Hsp90 function suggests that (*a*) measuring activity in normal tissue is not an informative surrogate for determining biological activity in the tumor and (*b*) the ''important'' Hsp90 client protein(s) to measure will likely vary from one tumor type to another. In the phase II trials that are currently under way or being planned, the contextual nature of Hsp90 function requires that development of useful pharmacodynamic assays to predict response will depend both on a thorough understanding of the role of multiple Hsp90 client proteins in each particular tumor type and on the technical ingenuity to measure them appropriately.

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