HSP90 as a target for cancer treatment

A literature review on the possibilities of the use of HSP90 inhibitors for treatment of different cancers

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16-04-2018

Abstract

HSP90, a major heat shock protein, plays a role in stabilization and activation of important proteins in tumors, such as the pro-survival factor Akt and oncogenic proteins like ErbB2 and BCR-ABL. Tumor cells can go in apoptosis when those proteins are degraded or not able to function properly. Therefore, inhibiting HSP90, causing degradation of those proteins, can result in apoptosis of tumor cells. However, the question is how this works and if this works in patients. Even though HSP90 inhibition did already show some promising results in clinical trials, it is necessary to consider the importance of tumor selectivity and toxicity. HSP90 inhibitors seem to specifically target tumor cells, due to the tumor cell 'addiction' to HSP90. Nonetheless, not all tumors respond to HSP90 inhibition and some tumors are able to use other pathways to evade the inhibition of HSP90. Specifically, tumors dependent on one specific oncoprotein that is completely dependent on HSP90 do respond to HSP90 inhibition. Therefore, screening of tumors for these characteristics is crucial for predicting a response to this treatment and so is crucial for further development of HSP90 inhibitors.

Introduction

Cells have to be able to stay healthy under various conditions. This means they must maintain homeostasis: a proper balance of reactions and molecules in the cells. Even more specific, they have to maintain proteostasis: the homeostasis of proteins. For the maintenance of this proteostasis, cells need chaperones, proteins that can help fold proteins and repair or dispose misfolded target proteins. Those chaperone target proteins are called clients.

One important group of chaperones is the group of heat shock proteins (HSPs). After stress, such as a heat shock, the cell activates the stress response, which results in expression of HSPs. However, HSPs are not only activated after stress but are also active under normal conditions in the cell (Lindquist, 1986). This means they play a way more important role than thought before, also under physiological conditions.

One of the major HSPs is HSP90, that affects more than 200 clients (Pratt, Morishima, & Osawa, 2008). It affects different pathways and has a variety of client proteins, such as growth factor receptors, metastable signaling proteins, mutated signaling proteins (p53 and v-SRC) and cell-cycle regulators (cdk4, cdk6) (Kamal, Boehm, & Burrows, 2004).

In tumor cells, HSP90 plays a role by affecting proteins important for the development of those tumors. This role is indirect, but HSP90 is necessary for survival of some tumor cells. More than 100 different HSP90 clients are known to play crucial roles in signaling pathways in human cancers (Kamal et al., 2004). For example, Akt has a pro-survival function and together with co-chaperone CDC37, HSP90 is required for Akt stability (Basso et al., 2002b).

Besides, these tumor cells have great genomic instability (Negrini, Gorgoulis, & Halazonetis, 2010). The imbalance due to the genomic instability has to be controlled by the protein quality control network, which is a second reason why HSP90 is important in tumors. The chances of proteins not being folded correctly are bigger in tumor cells than in healthy cells, which results in tumor cells being more dependent on repair and prevention mechanisms, such as the HSP90 machinery (Dai & Sampson, 2016). This higher dependency could be favorable when looking at therapeutic targets for tumor cells.

This genetical instability also allows tumor cells to quickly adapt and therefore escape from treatments, such as the commonly used chemotherapy and radiotherapy (Negrini et al., 2010). To tackle this problem, constant new treatments are required. A promising treatment for some non-responding tumors is the inhibition of HSP90, since HSP90 is involved in the different aforementioned pathways, all taking part in the acquired capabilities of cancer according to the 'Hallmarks of cancer' proposed by Hanahan and Weinberg. They suggest a theory dictating that 'the vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis' (Hanahan & Weinberg, 2000). HSP90 plays a major role in all of these six acquirements, by being necessary for activation of for aforementioned Akt, CDK4, SRC, and p53, that all play roles in the cancer hallmarks (Neckers, 2007).

Consequently, for this paper, it is examined how HSP90 can be used as a target for cancer treatment.

HSP90 and its co-chaperones

HSP90 consists of two monomers which will form the functional homodimer after dimerization (Wayne & Bolon, 2007). The protein can be in an open or in a closed state, the latter being

mediated by ATP binding and hydrolysis, causing conformational rearrangements. The two monomers consist of three domains, each with their own function. ATP binding is mediated by the amino-terminal domain (NTD), the binding of clients happens mostly in the middle domain (MD), and the dimerization occurs via the carboxy-terminal domain (CTD). The three domains are weakly linked, causing HSP90 to have great flexibility, and being able to undergo major conformational changes (Krukenberg, Street, Lavery, & Agard, 2011). These changes are mediated in a conformational cycle, which is in a constant equilibrium. The cycle (*figure 1*) starts with ATP binding to the NTD. This causes conformational changes in the NTD, and the 'lid' region closes over the ATP-binding region, resulting in the intermediate state. HSP90 then undergoes more rearrangements, which makes it go into the first closed state, with the two NTD regions dimerized. The last closed state is entered after the MD domains are associated, after which ATP hydrolysis can happen (Schopf, Biebl, & Buchner, 2017).

These conformational changes caused by ATP-binding are necessary for HSP90 function, shown by studies that inactivated this binding function (Ali et al., 2006). When ATP is not able to bind to HSP90 anymore, or cannot be hydrolyzed anymore, HSP90 loses its function and clients cannot be activated (Obermann, Sondermann, Russo, Pavletich, & Hartl, 1998).

This binding of clients is mediated by many different co-chaperones such as HOP, Cdc37, AHA1, and p23, that all have different functions, each important for regulating or specifying HSP90 activity (Schopf et al., 2017).

HOP is a co-chaperone that plays an important role in the HSP90 conformational cycle (*figure 1*). HOP preferably binds to the open state of HSP90. The closed state, in which ATP is bound, does not have any association with HOP. When HOP is bound to HSP90, it prevents HSP90 to go into the closed state and prevents it to bind p23, another co-chaperone (Johnson, Schumacher, Ross, & Toft, 1998). HOP has a second alternative function to transfer clients from HSP70 to HSP90. HSP70 is known to stabilize metastable and misfolded proteins, and after binding to HSP70, HOP is able to transfer the client from that HSP70 protein to HSP90, where it can be refolded into its active state (Wegele, Wandinger, Schmid, Reinstein, & Buchner, 2006).

P23 stabilizes the second closed state in the conformational cycle of HSP90 (*figure 1*). In this state, ATP is hydrolyzed, while the client
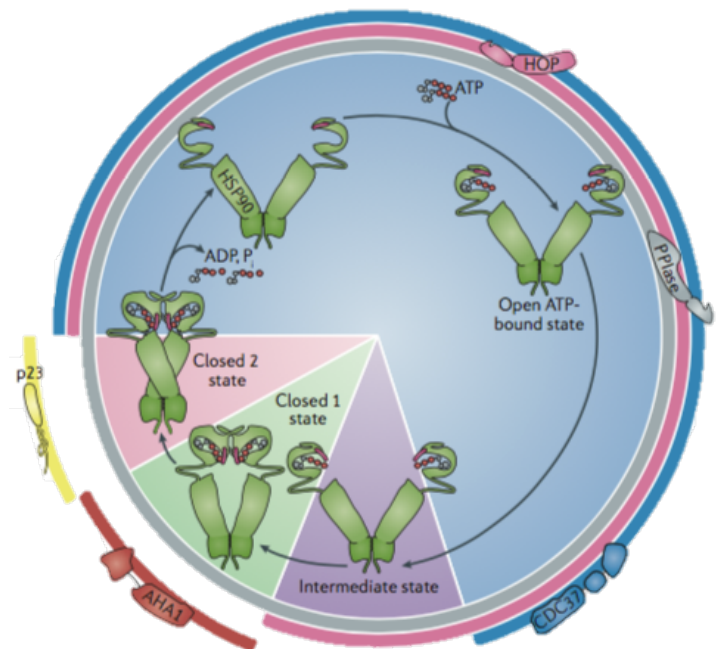

Figure 1: The HSP90 conformational cycle, including the different conformational states and co-chaperones affecting the cycle. ATP binding causes the 'lid' region to close, which results in the intermediate state. The first closed state is characterized by the NTD dimerization, after which a twist and of the monomers leads to the second closed state. Figure taken from Schopf et al., 2017

protein is getting activated (Lotz, Lin, Harst, & Obermann, 2003).

AHA1 is a co-chaperone that is able to stimulate the ATPase activity, by binding to the MD (Lotz et al., 2003). This means the closed state 1 is favored by AHA1(*figure 1*).

A co-chaperone that plays a major role in activation of HSP90 clients is Cdc37, that binds to the N-terminal domain of HSP90. Cdc37 can recognize kinases (one of the HSP90 client groups) that are not in their fully folded state, and recruit these to HSP90, to be assisted to fully fold (Taipale et al., 2012). Binding of Cdc37 causes an arrest in the conformational cycle (*figure 1*), causing HSP90 to stay in its open state and clients being able to bind. The majority

of HSP90 dependent clients are also dependent on Cdc37, indicating the major role of Cdc37 (Roe et al., 2004).

HSP90 substrates

Most of the HSP90 clients can be categorized into one of the following groups; steroid hormone receptors, kinases, E3 ubiquitin ligases or transcription factors (Taipale, Jarosz, & Lindquist, 2010). In this paper, there will be a particular focus on the kinases and transcription factors, considering their important roles in cancer and their parts played in promising HSP90 inhibitors in cancer. In fact, I will concentrate on four specific HSP90 clients, considering their involvement in tumors and effectiveness of HSP90 inhibition:
The first 2 are Akt and Cdk4. Akt is an HSP90 client and HSP90 is necessary for stabilization of Akt. It is involved in suppression of apoptosis and when inhibiting the binding between Akt and HSP90, apoptosis is induced (Lotz et al., 2003). This suggests that the binding between Akt and HSP90 is necessary for Akt function. Akt does not only inhibit apoptosis, it is also involved in growth, survival, and proliferation, and even angiogenesis in tumors (Manning & Cantley, 2007). Since HSP90 is necessary for activation of Akt, HSP90 also affects all these functions. Cyclin-dependent protein kinases (Cdks) are protein kinases that play a major role in the regulation of the cell cycle. Cdk4 takes part in the cell cycle regulation, specifically in the G1 phase. It is mediated by HSP90, and the co-chaperone Cdc37 is particularly important for the activation of Cdk4. Inhibition of HSP90 or Cdc37 results in a reduced half-life of Cdk4 (Stepanova, Leng, Parker, & Harper, 1996).
The second 2 are BCR-ABL and HER2 because those oncoproteins are affected by HSP90 and play a major role in respectively chronic myeloid leukemia and HER2-positive breast cancers. Some tumors are highly dependent on those oncoproteins, making BCR-ABL and HER2 dependent tumors interesting for HSP90 inhibition. This will be discussed more specifically later in this paper.
So, these clients of HSP90 all play an important role in some types of cancer, suggesting that HSP90 might also play an indirect role in the maintaining of the disease. The knowledge of these clients already suggests a potential therapeutic window for cancer treatment targeting HSP90.

Working mechanisms of HSP90 inhibitors

How the inhibition works
Inhibiting HSP90 is thought to be a potential new treatment for various types of cancer. Geldanamycin (GA) is an HSP90 inhibitor, that binds to the ATP binding site of HSP90, suggesting an inhibiting property due to the hindrance of ATP binding (Prodromou et al., 1997). This inhibition of ATP binding causes an arrest in the conformational cycle (*figure 1*). The 'lid' segment does not close anymore and HSP90 is unable to go into its intermediate or closed state. This closed state is necessary for activation of clients (Ali et al., 2006), suggesting that inhibiting ATP from binding causes clients to no longer get activated.
In a tumor, HSP90 is needed in non-stop chaperoning and stabilizing oncoproteins. This is caused by the constant binding of the co-chaperones to HSP90, resulting in a higher affinity form of HSP90. The complexes, created from the co-chaperones bound to HSP90, are necessary to be abundant in tumor cells, causing them to be able to handle the misfolding of the

oncoproteins, and rescuing tumor cells from potential cell death (Kamal et al., 2003). Thus, tumor cells need a higher affinity form of HSP90 to chaperone oncoproteins.

GA did not go into clinical development, due to its low solubility, and hepatotoxicity (Scaltriti, Dawood, & Cortes, 2012). To overcome the problems with GA, a new compound was developed, called 17-allylamino-17-demethoxygeldanamycin (17-AAG). This inhibitor also binds to the ATP binding site. Even though this compound solves the solubility problem, it might still be hepatotoxic. The possible toxicities of HSP90 inhibition and ways to potentially overcome these will be discussed later in this paper.

The inhibition specificity

To function as a cancer treatment, HSP90 inhibitors have to be specific to cancerous cells. While they target tumor cells, healthy cells need to be unaffected. Even though HSP90 is highly abundant in normal cells, 17-AAG specifically targets HSP90 in tumor cells (Chiosis et al., 2003). The reason for this specificity is most likely caused by intrinsic differences between normal HSP90 and tumor HSP90. A research published in 2003 showed that tumor cell HSP90 has a greater binding affinity to 17-AAG than normal HSP90, with tumor HSP90 being in a higher affinity complex with different co-chaperones. A recent study suggests a reason why tumor cells have this higher affinity. They show that the mitotic checkpoint kinase Mps1 causes phosphorylation of HSP90, which results in a reduction of ATPase activity but a promotion of HSP90 association with kinase clients. Different tumors show higher levels of this Mps1 (Woodford et al., 2016).

Two things are important considering tumor specific HSP90 inhibition effects: tumor cells are more dependent on HSP90 and HSP90 inhibitors have a greater affinity to tumor cell HSP90. This causes only tumor cells. to be affected and HSP90 inhibition an interesting new target for therapy.

Cellular consequences of the inhibition

The major cellular consequence of inhibiting HSP90 is the degradation of HSP90 client proteins, such as ErbB2. The proteome causes this degradation, after polyubiquitination of the protein (Mimnaugh, Chavany, & Neckers, 1996). A factor responsible for the regulation of this ubiquitination and degradation is C terminus of HSC70-Interacting Protein (CHIP), an E3 ubiquitin ligase. This protein interacts with HSP90 and induces ubiquitination of the target protein, following the proteasomal degradation (Connell et al., 2001). When used in tumors that are specifically dependent on one oncogenic protein, such as ErbB2, degradation of this protein usually leads to death of the tumor cells (Xia et al., 2006).

However, the inhibition of HSP90 may not only cause direct toxicity but also (indirectly) enhance sensitivity to radiotherapy or chemotherapy.

Direct and indirect effects

Direct toxicity

One example of promising results after HSP90 inhibition is shown in BCR-ABL positive chronic myeloid leukemia (CML) cells. These cells are mostly resistant to all commonly used therapies and therefore new ways of targeting are required. The cells are resistant because of their ability to evade apoptosis induced by anticancer treatments, due to the BCR-ABL fusion protein, that has a constant tyrosine kinase activity (Druker & Lydon, 2000). Selective inhibitors of this protein already exist, but different types of leukemia are also found to be resistant to these. Targeting the BCR-ABL tyrosine kinase causes resistance because mutations

occur in the specific binding site for the inhibitor (Druker, 2006). Since BCR-ABL is an HSP90 client, inhibiting HSP90 in those cells may have an antitumor effect. It is found that inhibiting HSP90 with geldanamycin causes a BCR-ABL depletion and almost a maximal toxicity. Additionally, it sensitizes the tumor cells to the chemotherapeutic doxorubicin and it even protects healthy cells to apoptosis induced by this drug (Blagosklonny et al., 2001). It is shown that not only BCR-ABL is affected in CML cells but also decreased Akt is measured, even independent from the decrease in upstream BCR-ABL (George et al., 2005). The reduction of survival and growth by HSP90 inhibitors might be due to BCR-ABL degradation as well as the Akt degradation. The synergy between inhibition of these two pathways is likely to play a role in the apoptosis of the CML cells (George et al., 2005). These results indicate an increased therapeutic window. They also suggest potentially fewer side effects for CML patients, considering the protection of healthy cells to apoptosis and sensitization to chemotherapy. Additionally, targeting HSP90 instead of BCR-ABL overcomes the problem of resistance against BCR-ABL inhibitors, since it does not directly target the mutated protein.

Another well-responding protein to HSP90 inhibition is HER2/ErbB2. This protein is highly overexpressed in 20% of the breast cancers (Scaltriti et al., 2012), and dependent on HSP90 (Scaltriti et al., 2012). The tumor is dependent on the HER2 protein, making it the perfect candidate for HSP90 inhibition. Nowadays, HER2 inhibitors are used as a drug to target HER2 specifically, but some tumors are resistant to them, causing a great need for new ways to target this type of cancer. The resistance to HER2 tyrosine kinase inhibitors can also be caused by mutations of the tyrosine kinase domain, which is why the inhibitors are not able to bind anymore (Nielsen, Andersson, & Kamby, 2009). HSP90 inhibition in human breast cancer cells, that overexpress HER2 and are resistant to HER2 antibodies, results in HER2 degradation. The degradation of HER2 causes inhibition of the Akt signaling pathway, resulting in induction of apoptosis and inhibition of tumor growth in HER2 overexpressing breast cancers (Chandarlapaty et al., 2010). This suggests that HSP90 is a promising target for HER2 antibody resistant breast cancer cells.

Additional to the two explained examples, various other HSP90 clients might be suitable as a therapeutic target for HSP90 inhibition. For example BRAF, mutated in malignant melanomas (Paraiso et al., 2012), or CKIT, that is, when mutated, associated with gastrointestinal stromal tumors (Rubin et al., 2001) These mutated or overexpressed protein-dependent tumors are in most cases suitable for HSP90 inhibition and their therapeutic mechanisms are all similar to the two explained above (Paraiso et al., 2012; Rubin et al., 2001).

Radio-sensitization and chemo-sensitization
Not all tumors are fully dependent on one HSP90 client protein. However, some tumors that are not, still respond to HSP90 inhibition by gaining sensitivity to radiotherapy or chemotherapy.

Chemo-sensitization
The Akt pathway is activated in some tumors as a pro-survival pathway and, therefore, causes resistance to treatments in several tumors. An example of this is ovarian cancer that develops resistance to cytotoxic drugs. Research found that by inhibiting HSP90, ovarian cancer is re-sensitized to cytotoxic drugs (Sain et al., 2006). However, this research does not go into detail why sensitization happens. One mechanism explaining this re-sensitization is the degradation of Cdk4 and Cyclin D. Cyclin D/Cdk4 plays a crucial role in the cell cycle and downregulating them causes G1 cell cycle arrest. Cdk4 is an HSP90 client and by inhibiting HSP90, a less Cdk4 expression is shown (Basso et al., 2002a). Cyclin D is not a client of HSP90, yet is less

expressed after HSP90 inhibition. This is caused by the degradation of Akt after HSP90 inhibition, considering the fact that Akt is an HSP90 client and Akt is required for the translation of cyclin D. This explains the decreased expression of cyclin D after HSP90 inhibition (Basso et al., 2002b). Thus, the inhibition of HSP90 can cause downregulation of Cdk4 and Akt, resulting in downregulation of cyclin D, which results in a G1 cell cycle arrest. This cell cycle arrest might sensitize the tumor cell to cytotoxic drugs.

Because HSP90 is also present in healthy cells, inhibition might sensitize those cells to cytotoxic drugs as well, which would completely cancel out the effects. However, HSP90 is abundant in a greater affinity form in tumor cells, so the sensitization would most likely only occur in tumor cells.

Radio-sensitization
HSP90 inhibition can also cause enhanced radio-sensitivity in tumor cells. The possible mechanism responsible for this might involve abrogation of cell cycle caused by radiotherapy (Bull et al., 2004). Chk1 and Wee1 are proteins necessary for G2/M cell cycle checkpoint. Both proteins are HSP90 clients and HSP90 inhibition by 17-AAG causes decreased levels of the two. Decreased Chk1 and Wee1 levels result in the G2/M cell cycle checkpoint abrogation and less DNA-damage repair (Tse, Sheikh, Alan, Chou, & Schwartz, 2009). When DNA-damage is induced by radiotherapy, the reduced ability to repair DNA could cause more cell death. HSP90 inhibitors might, therefore, have a sensitizing effect on radiotherapy.

Analysis of clinical trial results so far

The last ten years, clinical trials have been done to examine the efficiency and toxicity of HSP90 inhibitors. Some results of these trials are highly promising and seem to give new options for patients with tumors unable to be cured. On the other hand, different clinical trials did not show such promising results (Pacey et al., 2012; Ronnen et al., 2006). This could be because the dose or drug frequency was not high enough. However, higher dose or frequency turned out to be toxic in patients and causing major side effects. Different other inhibitors have been developed to overcome these toxicities and resulted in higher tolerable maximum doses and drug frequencies (Modi et al., 2011).

Especially in the last few years, promising trials have been done, with less toxicity and higher response rates.

	Response rate	Median duration of response	Toxicities
HER2 dependent breast cancer	22%	147 days	Diarrhea, fatigue, nausea, and headache
Multiple myeloma	39,2%	5,6 months (168 days)	Diarrhea, fatigue, and neutropenia, nausea, and thrombocytopenia
Acute myeloid leukemia	23,5%	-	Neutropenic fever, fatigue, nausea, and diarrhea
Small cell lung cancer	25%	137 days	Diarrhea, nausea, fatigue, and transaminitis

Table 1: results of different clinical trials

A phase 2 study in 2011 showed an antitumor effect of 17-AAG on the aforementioned HER2-dependent breast cancer. This trial is done with patients treated with anti-HER2 antibody, who however do not respond (anymore) to this treatment. The trial showed promising results as

shown in *table 1* (Modi et al., 2011). These results are in line with the expectations of HER2 being highly suitable for HSP90 inhibition.

Another clinical trial is done with HSP90 inhibitors in patients with relapsed/refractory multiple myeloma. This study uses the combination between an HSP90 inhibitor and bortezomib, a proteasome inhibitor. This combination resulted in modest anti-myeloma activity and was well tolerated (Cavenagh et al., 2017).

The outcomes of a trial with patients with acute myeloid leukemia seem promising as well. The patients were treated with an HSP90 inhibitor, alvespimycin, a geldanamycin derivate. The drug was well tolerated and HSP90 inhibition was measured. Apoptosis of the leukemia cells was shown, just as an antileukemia activity in three of the seventeen patients, however, the sample size was very small (Lancet et al., 2010). To determine how efficient these HSP90 inhibitors cause an antileukemic effect, more research with larger groups is needed.

A recent paper published in March 2018 shows a phase Ib/II study in patients with relapsed/refractory small cell lung cancer with HSP90 inhibition in combination with chemotherapy. There is preliminary evidence shown of an antitumor effect after treatment with ganetespib and doxorubicin (Di Lorenzo et al., 2018). The results of this study, however, is obtained by a patient group consisting of 8 patients, which means more research is necessary for further conclusions.

As indicated by the four studies above, HSP90 inhibitors seem to have promising effects on different tumors. However, to be able to say more about the effects of the inhibitors, more research is crucial, especially research conducted with more patients.

Discussion

HSP90 is found to be crucial for activating and stabilizing target proteins that play a major role in tumors. HSP90 plays an important role in tumor cell-survival and this essential role of HSP90 is a motivation for different studies to examine the effects of inhibiting HSP90 in cancer cells. Inhibiting HSP90 can result in direct toxicity, usually in tumors that are dependent on a specific oncoprotein, which is an HSP90 client. Inhibition, in that case, results in degradation of the client and therefore apoptosis of the tumor cell. These tumors also show promising results in clinical trials, like a trial with HER2-dependent breast cancer patients (Modi et al., 2011).

However, the working of inhibiting HSP90 might not be as simple as was thought, and more research is needed to examine the effects and mechanisms of HSP90 inhibition in different tumors. The clinical trials, in my opinion, do not yet have the dramatic outcome expected by the preclinical trials. It might have been underestimated how complex the heat shock response is and how many mechanisms the tumor cell has to solve the loss of HSP90 function. Apart from that, maybe the tumor environment plays a role in solving HSP90 inhibitory effects since some tumor cells seemed to be affected by inhibition but did not show any effect in the clinic. It might be interesting to look into the reason why HSP90 inhibitors do kill tumor cells in vitro but do not have an effect in patients with the same kind of tumor.

I think it may be convenient to look into tumors that are dependent on proteins completely dependent on HSP90. Those tumors have great potential to experience antitumor effects by HSP90 inhibition. A screening of those specific tumors, to know which ones will probably respond to inhibition, might be a way to raise HSP90 inhibitor effectiveness. In my opinion, especially this part of the HSP90 inhibition research is promising.

A concern I have with regard to HSP90 inhibition is the possible resistance to this drug. Tumors could possibly develop mutations, causing HSP90 inhibitors to not be able to bind HSP90 anymore and clients to not get degraded. More long-term research is necessary to find out the possible resistance to HSP90 inhibitors in tumor cells.

To conclude, HSP90 could be used as a target for cancer therapy. However, this might only regard specific kinds of tumors. For HSP90 inhibitors to be effective, tumor screening is required to assess if it will respond to the therapy.

Perspectives: alternative targets

Most HSP90 inhibitors are effective by binding to the ATP-binding pocket in the N-domain of HSP90. Recent studies, however, search for alternative ways to inhibit HSP90. A potential new way to target HSP90 is to aim at the interactions between HSP90 and its co-chaperones. As Cdc37 facilitates recruitment of client proteins to HSP90, this co-chaperone has gained interest as a target for therapy. A research has shown that silencing Cdc37 in prostate cancer cells causes a reduction of activity of clients and a growth inhibition (Gray, Stevenson, & Calderwood, 2007). These effects are due to the degradation of clients by the proteasome and apoptosis with HSP90 inhibitors (Smith, Clarke, de Billy, & Workman, 2009). Targeting Cdc37 instead of HSP90 itself might be preferable, as HSP90 inhibition can result in a heat shock response, which inhibits antitumor efficacy (Bagatell et al., 2000). Thus, targeting Cdc37 does have an antitumor effect, but does not induce the heat shock response and might, therefore, be a promising target instead of HSP90.

While silencing Cdc37 causes client degradation, it is made clear that inhibition of the direct interaction between HSP90 and Cdc37 does not affect chaperone function. In fact, inhibiting the binding between HSP90 and Cdc37 resulted in an increase in HSP90 client Cdk4 expression and interaction between Cdk4 and HSP90 (Smith et al., 2015). So, binding between HSP90 and Cdc37 is not necessary for Cdc37 to efficiently recruit client proteins to HSP90. This means targeting Cdc37 may be a promising alternative target but targeting the Cdc37-HSP90 interaction will not be sufficient.

Not only Cdc37 but also AHA1 has been found to be a co-chaperone that could be targeted. In a recent study, an inhibitor was found that is capable of blocking a crucial interaction between AHA1 and HSP90. This inhibition prevented the activation of AHA1-HSP90 dependent client proteins (Stiegler et al., 2017).

These promising results of research on Cdc37 caused more interest in co-chaperone targeting to inhibit HSP90. A lot more research is needed, not only on Cdc37 but also looking into other co-chaperones of HSP90. Even though there is still a lot unknown, these alternative ways of targeting might be very promising.

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