Medical Oncology (2022) 39:180
https://doi.org/10.1007/s12032-022-01777-x

REVIEW ARTICLE

Combination of AURKA inhibitor and HSP90 inhibitor to treat breast cancer with AURKA overexpression and TP53 mutations

Fuping Wang[1] · Haotian Zhang[1] · Haitao Wang[2] · Tian Qiu[3] · Binghong He[1] · Qiong Yang[1]

Received: 9 May 2022 / Accepted: 16 June 2022

Abstract

Breast cancer is the most common cancer among women worldwide. Researches show that Aurora kinase A (AURKA) is highly expressed in approximately 73% of breast cancer patients, which induces drug resistance in breast cancer patients and decreases the median survival time. AURKA regulates spindle assembly, centrosome maturation, and chromosome alignment. AURKA overexpression affects the occurrence and development of breast cancer. Besides AURKA overexpression, heat shock protein 90 (HSP90) maintains the survival and proliferation of tumor cells by stabilizing the structure of oncoproteins, including P53 mutants (mtP53). TP53 mutations accounted for approximately 13%, 40%, 80%, 33%, 71%, and 82% of luminal A, Luminal B, Luminal C, normal basal-like, HER2-amplified, and basal-like breast cancers, respectively. TP53 mutation can aggravate cell genome instability and enhance the invasion, migration, and resistance of cancer cell. This review describes the research status of AURKA and HSP90 in breast cancer, summarizes the structure, function, and the chaperone cycle of HSP90, elaborates the interrelation between HSP90, mtP53, P53, and AURKA, and proposes the combination of HSP90 inhibitor and AURKA inhibitor to treat breast cancer. Targeting AURKA and HSP90 to treat cancer with AURKA overexpression and TP53 mutations will help improve the specificity and efficiency of breast cancer treatment and solve the problem of drug resistance.

Keywords Heat shock protein 90 · Aurora kinase A · P53 mutants · Breast cancer · Drug resistance

Introduction

According to the report of the International Agency for Research on Cancer, Female breast cancer has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. It is the fifth leading cause of cancer mortality worldwide, with 685000 deaths [1]. Breast cancer is a heterogeneous tumor, with substantial genotypic and phenotypic diversity. Through study of human gene expression profiles, breast cancer can be classified into six subtypes, including luminal A, luminal B, luminal C, normal basal-like, epidermal growth factor receptor 2-amplified, and basal-like cancers [2]. According to the immunohistochemical expression of estrogen receptor (ER) or progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), breast cancer was classified into four subtypes: $ER^+PR^+HER2^+$, $ER^+PR^+HER2^-$, $ER^-PR^-HER2^+$, and $ER^-PR^-HER2^-$ [2]. Breast cancer described as $ER^-PR^-HER2^-$ subtype belongs to the basal-like subtype, also known as triple-negative breast cancer (TNBC) [3]. Notably, TNBC accounts for 15–20% of all breast cancers [4]. TNBC is an aggressive breast cancer subtype that carries a high risk of developing distant metastasis, so TNBC urgently needs new and effective treatment [5]. Metaplastic breast carcinoma (MPBC) accounts for 0.2–5% of all breast cancers and is typically very aggressive, with worse clinical outcomes than TNBC [6]. Comprehensive genomic profiling was reported in the largest dataset of MPBC, which revealed a wide variety of genomic alterations

✉ Qiong Yang
yangqiong@bnu.edu.cn

1 Beijing Key Laboratory of Resistant Gene Resources and Molecular Development, College of Life Sciences, Beijing Normal University, Beijing 100000, China

2 Department of Hematology, Fourth Medical Center, Chinese PLA General Hospital, Beijing 100000, China

3 Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100000, China

Published online: 07 September 2022

with a high prevalence of TP53 (65%) mutations, which may represent potential therapeutic targets [7]. Treatments of breast cancer includes surgery, radiotherapy, endocrine therapy, chemotherapy, and targeted therapy. MPBC is routinely treated with chemotherapy, surgery, and radiation, but outcomes remain poor [8]. While treatment strategies that combine surgery with adjuvant chemotherapy improve survival rates, a significant portion of patients eventually acquire resistance to chemotherapeutic agents. Current metastatic therapies are expensive, often toxic, and doomed to the eventual development of drug resistance [9]. Thus, strategies to overcome chemoresistance are urgently needed, such as effective targeted therapy.

AURKA, an evolutionarily conserved serine/threonine kinase, is great significance for the normal progress of the cell cycle [10]. It mainly includes two domains: the N-terminal modulatory domain and the C-terminal catalytic domain. At the N-terminus, there are two functional regions, A-Box and B-Box, which are related to the degradation of AURKA. At the C-terminus, the phosphorylation level of the C-terminal threonine is related to the activation of AURKA [11]. AURKA regulates mitotic entry, spindle assembly checkpoint, centrosome maturation, centrosome separation, and chromosome alignment [12]. In breast cancer, AURKA is highly expressed in approximately 73% of breast cancer patients, which induces drug resistance in breast cancer patients and decreases the median survival time [13]. Recent studies suggest that the kinase activity of AURKA is responsible for chemoresistance [4, 14].

In malignant cells, HSP90 expression is constitutive, which is 2–10 times that of normal cells, suggesting that it plays an important role in the survival and growth of cancer cells [15]. It was found that the interaction of the mtP53 DNA-binding domain with the chaperone HSP90 is important for the stability and activity of mtP53 in vivo [16]. TP53 deletion or mutation can also aggravate the host cell genome instability, increase the risk of cancer, and enhance the invasion, migration and resistance of cancer cells, which is an important reason for the poor prognosis of patients [17]. TP53 mutations accounted for approximately 13%, 40%, 80%, 33%, 71%, and 82% of luminal A, Luminal B, Luminal C, normal basal-like, HER2-amplified, and basal-like breast cancers, respectively [2]. P53 is encoded by the TP53 gene, which suppresses cancer primarily by protecting genome stability. It includes six domains: two N-terminal transactivation domains, a proline-rich domain, a central DNA binding domain, a tetramerization domain, and a C-terminus Modulatory domain [18]. TP53 is the most frequently mutated gene across all cancer types, and around 50% of human cancers harbor mtP53 [19]. TP53 mutations are associated with de novo resistance to doxorubicin in breast cancer patients. Because TP53 mutations are diverse in their sequence context, position, and structural impact, the drugs research for mtP53 have high cost and little applicability. Moreover, there are different mtP53 in the same cancer, resulting it more difficult and less effective to develop drugs for mtP53.

This review summarizes the structure, function and chaperone cycle of HSP90, analyzes the interrelation between HSP90, mtP53, P53, and AURKA, and proposes targeting HSP90 and AURKA to treat breast cancer with AURKA overexpression and TP53 mutations, which will help to improve the specificity and efficiency of breast cancer treatment and solve the problem of drug resistance. This review will promote the research of AURKA, HSP90 and P53, and bring new strategies for solving the problem of drug resistance and improving the effectiveness of cancer treatment.

AURKA and breast cancer

AURKA is overexpressed in 96% of human cancers and is considered an independent marker of poor prognosis. While the majority of tumors have elevated levels of AURKA protein, few have AURKA gene amplification [20]. As mentioned above, about 73% of breast cancer patients have high AURKA expression, which induces drug resistance in breast cancer patients and reduces the median survival time [13]. Increased expression of AURKA is observed in prevalent cancers and associated with poor prognostic and the development of drug resistance. In addition, some chemotherapy drugs can reduce the expression of this gene [21]. Studies in different cancer cell lines have shown that AURKA overexpression changes the sensitivity to microtubule drugs and leads to chemotherapy resistance [22, 23]. Abnormal expression and location of AURKA regulates the occurrence and development of tumors through various mechanisms. The main pathways include: accelerating tumor cell cycle progression, activating tumor cell survival or anti-apoptotic signaling pathways, inducing tumor cell genome instability, increasing tumor cell epithelial-mesenchymal transition and promoting the formation of tumor stem cells with self-renewal ability [11]. The carcinogenic effects of AURKA may be different in different types of cancer [24]. In breast cancer, one mechanism is AURKA and FOXM1 form a positive feedback loop and jointly regulating the proliferation of breast cancer stem cells. Kinase-dead AURKA can effectively transactivate the FOXM1 promoter through a forkhead response element, whereas FOXM1 can activate AURKA expression at the transcriptional level in a similar manner [25]. AURKA regulates the proliferation, infiltration and metastasis of breast cancer cells, so AURKA inhibitors can specifically treat breast cancer with AURKA overexpression.

HSP90 and breast cancer

HSP90 is considered as an important facilitator for the maintenance of malignant phenotype, because cancer cells

generally use the chaperone machinery of HSP90 for their survival advantage [26]. HSP90 expression is high in breast cancer cell lines and human breast cancer [27]. HSP90 is required for stability of proto-oncogenes, which is important for breast cancer growth and survival, including ER, PR, and HER2 [15]. HSP90 combines with mtP53 through conformational specificity, leading to compound accumulation of mtP53, prolonging half-life, inhibiting apoptosis, and promoting tumor formation [28]. The main role of HSP90 in cancer is not only reflected in the stability of mtP53, but also in the development of tumor initiating cells [29]. Early research found that the mRNA level of HSP90 in breast cancer tissues was significantly higher than that in non-cancerous tissues, and it was closely related to the expression index of proliferating cell nuclear antigen. Poorly expressed cancer tissues are significantly higher than well-differentiated breast cancer tissues [30]. Currently, blocking the function of HSP90 has shown encouraging results in clinical trials for several cancers including breast cancer [30]. Therefore, HSP90 inhibitors are effective in the treatment of breast cancer with P53 mutants.

HSP90 structure and function

The HSP90 family is divided into five subfamilies: cytoplasmic HSP90A, endoplasmic reticulum HSP90B, mitochondrial TNFR-related protein, chloroplast HSP90C, and bacterial high-temperature protein G. Cytoplasmic HSP90 is the most important of the five HSP90 subfamilies, with three major conserved domains: N-terminal domain (NTD), middle domain (MD), and C-terminal domain (CTD). In eukaryotic cells, there is a charged junction region between NTD and MD, which facilitates HSP90 to change the conformation and bind to co-chaperones. NTD binds to adenine nucleoside triphosphate, known as a nucleotide binding site, and mediates the chaperone function of HSP90. MD binds to co-chaperones to act on client proteins and regulate molecular chaperone function. CTD is responsible for HSP90 dimerization and also contains a special motif, MEEVD, which binds co-chaperones. The mammalian cytoplasmic HSP90 is classified into HSP90α and HSP90β, based on whether it contains glutamic acid fragments [31]. In human cytoplasm, HSP90α is abundantly expressed after stimulation and HSP90β is constitutively expressed. Cytoplasmic HSP90 mainly exists as homodimer αα or ββ, HSP90β is the major form of HSP90 involved in normal cellular functions, such as maintenance of the cytoarchitecture, differentiation, and cytoprotection. The amino acid sequence homology of HSP90α and HSP90β is about 85% [26].

Cytoplasmic HSP90 guides the normal folding, localization, and degradation of critical regulators of cell growth, differentiation, and survival [32]. HSP90 plays a molecular chaperone role by relying on ATP to cycle between closed and open conformations. When NTD binds to ATP, the conformation of HSP90 changes, CTD and MD bind to the co-chaperones that carry the client protein, and the two dimers of NTD form a closed state due to binding to ATP, allowing the HSP90 client protein to function in a stable state; when the NTD-bound ATP is hydrolyzed to ADP, the conformation of HSP90 changes [33]. HSP90 can stabilize the structure of these client proteins to ensure proper function and stress response. Extracellular HSP90 includes HSP90 bound on the cell surface, HSP90 released by the cell, and HSP90 secreted by the cell. Extracellular HSP90 is emerging as a pivotal regulator of cell motility, invasion, and metastasis [34]. HSP90 is closely related to the occurrence and development of breast cancer, and it stabilizes the structure of oncoproteins and maintains the survival and proliferation of tumor cells. Therefore, the degradation of oncogenic proteins by inhibiting the function of HSP90 is a promising method for treating tumors.

HSP90 chaperone cycle

Because HSP90 ATPase activity plays a decisive role, HSP90 chaperone cycle is also called HSP90 ATPase cycle [35]. For different client proteins, there are certain differences in the conformational changes of HSP90, the types of co-chaperones involved, and the time of entry in the HSP90 chaperone cycle. These differences have led to HSP90 being able to stabilize different client proteins in a variety of manners, but the HSP90 chaperone cycle of the same type of client protein is basically similar. Figure 1 illustrates the HSP90 chaperone cycle and substrate degradation using the kinase CRAF and the transcription factor glucocorticoid receptor (GR) as examples. HSP90 exists as an open homodimer in cells. When the ATP is bound to the NTD of HSP90, the N-terminus of HSP90 is brought closer to each other. When the client protein is the kinase CRAF, Cdc37 first binds CRAF. Then Cdc37 binds to the NTD of HSP90 activated by ATP. The conformation of HSP90 changes after binding Cdc37, which enables PP5 to bind to the MD and MEEVD of HSP90. The conformation of HSP90 changes again and Aha1 binds to the HSP90 complex, resulting in a change in the kinase conformation to stable. With the release of the phosphate group, the co-chaperones, CRAF and HSP90 separated, and HSP90 returned to the open state. If the kinase CRAF folds abnormally, it causes the E3 ligase HECTD3 to bind to CRAF, causing the abnormal CRAF to be degraded by the ubiquitin–proteasome pathway [36, 37]. When the client protein is the GR, the Hop protein binds to the MEEVD, CTD, and MD of ATP-activated HSP90, and the conformation of HSP90 does not change significantly. HSP70 and HSP40 bind to GR and interact with Hop, the conformation of HSP90 does not change significantly. Then a molecule of PPlase binds to the HSP90 molecule that does

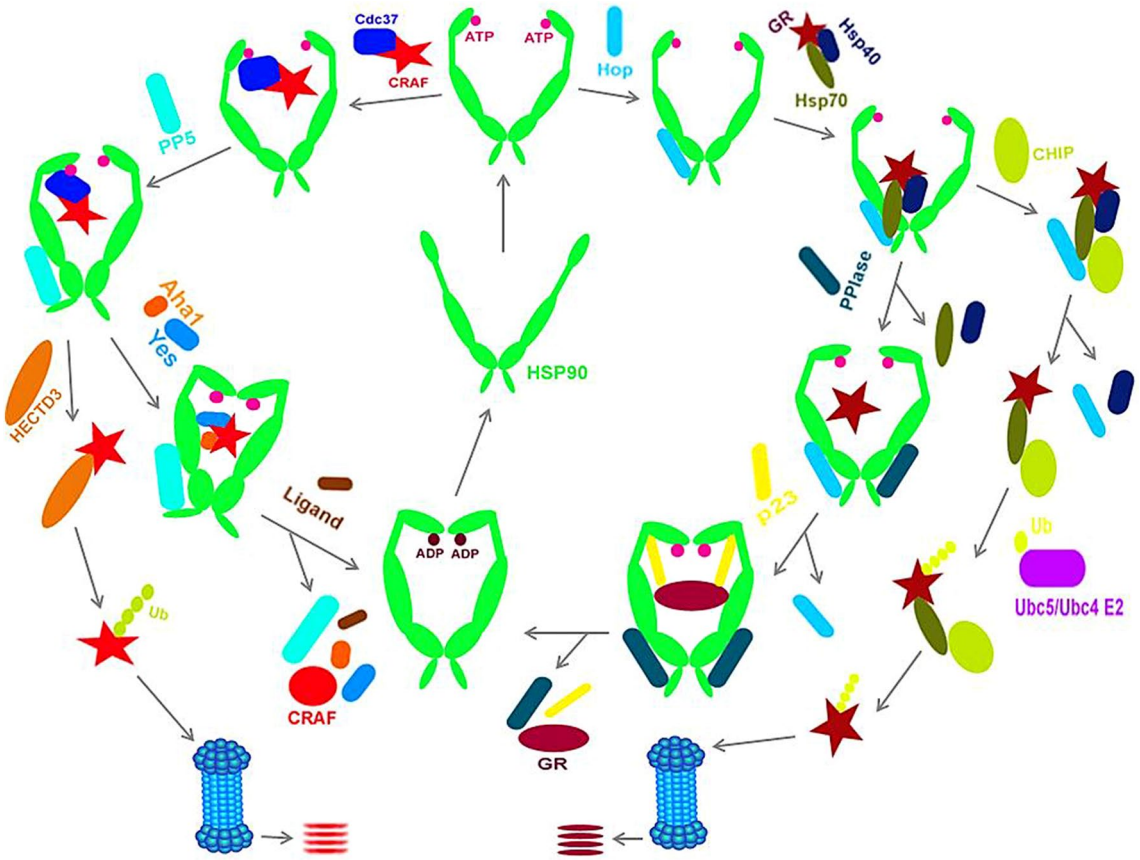

Fig. 1 HSP90 chaperone cycle of CRAF (left side) and GR (right side). HSP90 co-chaperones regulate the formation of client complexes with the HSP90 dimer and affect the conformational changes in the HSP90 dimer

not bind to Hop, resulting in the separation of HSP70 and HSP40 from the HSP90 complex. Subsequently, P23 binds to the NDT of HSP90, and the Hop is separated from the HSP90 complex. HSP90 binds to the second PPIase molecule, which causes the GR conformation to be changed and stabilized. With the release of the phosphate group, the co-chaperones, GR and HSP90 are separated, and HSP90 returns to the open state [38]. If GR folds abnormally, it will cause the C-terminus of the HSP70 interacting protein (CHIP) to bind with HSP70, which will cause the GR complex to leave HSP90, the GR complex will dissociate, and then GR will be ubiquitinated by Ubc5/Ubc4 E2 binding enzyme and CHIP. Finally, the abnormal GR is degraded by the ubiquitin–proteasome pathway [39].

The interrelation of HSP90, mtP53, P53, and AURKA

HSP90 maintains P53 activation status through the HSP90 chaperone cycle and regulates P53 degradation through the ubiquitin–proteasome system [40]. Study has shown that HSP90 and P53 are combined through a number of short-term interactions, and finally adopt a molten globular state [41]. This mutant allele produces the abnormal protein mtP53, which not only loses the tumor suppressing function, but also promotes the malignant progression, invasion, metastasis, and drug resistance of cancer, leading to reduced survival of patients and mice. Stability of mtP53 in tumor cells is a prerequisite for obtaining oncogenic function. The reason for stability is that the HSP90/HDAC6 chaperone mechanism protects mtP53 from degradation by CHIP and HDM2 [42]. Both P53 and mtP53 are mediated by HSP90, but compared to P53, the abnormally conformed mtP53 needs to form a complex with HSP90 to prevent aggregation, and the interaction between mtP53 and HSP90 blocks the E3 ligase activity of endogenous HDM2 and CHIP [28]. In normal cells, it is mainly HDM2 that binds P53 to degrade it. In tumor cells, MDM2 may be mutagenized and inactivated in the trimer complex of the mutant P53-MDM2-HSP90, and proposes that HSP90 binding may mask the ARF binding site is thus inhibited by its ligase function [28, 43]. Because there are too many P53 mutants, it is a good solution to treat mtP53 tumors by inhibiting HSP9 activity, so that mtP53 is degraded. Ganestespib is a highly effective synthetic HSP90 inhibitor, killing cancer cells containing

mutant P53 (but not wild-type P53) is significantly more effective than 17AAG [40]. In addition to stabilizing oncogene activity in tumors, HSP90 also participates in the evolution of tumor drug resistance [44]. HSP90 can inhibit the activity of the proto-oncogene HDM2 and lead to the accumulation of mtP53, so inhibition of HSP90 will reduce the tumor cell activity of mtP53 [28, 45]. In human cancer cells, mtP53 can interact with HDM2, but mtP53 lacks ubiquitination and extremely stable. The reason is the activation of HSP90 and the inhibition of HDM2 and CHIP activity. Compared to HDM2, ubiquitination degradation of mtP53 is mainly mediated by CHIP, so inhibition of HSP90 can significantly reduce mtP53 in TP53 mutation tumors. Treatment of cancer cells with 17-AAG leads to the degradation of different P53 mutants, including R175H, L194F, R273H, and R280K, and the reduced viability of cancer cells containing these P53 mutants [28]. CHIP is also an E3 ligase for HSP70 and HSP90 [46]. Recent studies have confirmed that CHIP can mediate the ubiquitination of HSP90 on 13 lysine residues such as K107, K204, K219, K275, K284, K347, K399, K477, K481, K538, K550, K607, and K623. Polyubiquitin chains are linked via K6, K11, K48, and K63 [46].

Activated AURKA regulates the expression of P53 by inducing the phosphorylation of P53 and the phosphorylation site of P53 are Ser315, Ser215, and Ser106. P53 phosphorylation on Ser315 promotes the binding of MDM2 to P53 and increases the degradation of P53 [47]. P53 phosphorylation on Ser215 results in weakened P53 binding to DNA, loss of transactivation activity, decreased P21 expression, binding of CDK2 and phosphorylated Rb protein (pRb) in the nucleus, and enhanced AURKA expression [48]. P53 phosphorylation on Ser106 weakens the binding of P53 to MDM2, reduces the ubiquitination of P53, and prolongs the half-life of P53 [49]. AURKA and P53 form a feedback loop. P53 negatively regulates AURKA expression after transcription and translation [50]. The important function of P53 is to bind to the promoter region of P21 and promote the expression of P21. P21 binds to CDK2 in the nucleus and inhibits the expression of AURKA. P53 can inhibit the phosphorylation of AURKA, thereby inhibiting AURKA activation. After mutant MDM2 fails to bind to P53 or MDM2 is inhibited by RNA interference, the damaging effect of AURKA on P53 is eliminated. Silencing AURKA can reduce the phosphorylation of P53 at Ser315, enhance the stability of P53, and achieve cell cycle arrest at G2-M [51]. In prostate small cell neuroendocrine cancer, mtP53 promotes the expression of miR-25, thereby inducing AURKA overexpression to make the disease worse [52]. These findings suggest that the relationship between HSP90, mtP53, P53, and AURKA may be important in anti-cancer treatment. The interaction between HSP90 and AURKA is closely related to tumor development and drug resistance. Therefore, in the study of tumor drugs, we need to consider the interaction of AURKA and P53 [51]. The interaction between HSP90, mtP53, P53 and AURKA is summarized in Fig. 2, which will bring new ideas for solving the problem of drug resistance and improving the effect of cancer treatment.

AURKA inhibitors

AURKA inhibitors can be divided into two categories: specific AURKA inhibitors, such as MLN8054, MLN8237 (Alisertib), and ENMD-2076; broad-spectrum Aurora kinase inhibitors, such as AMG-900, PF-3814735, AT9283 and Curcumin (Table 1). With the development of AURKA inhibitors, it has been found that the antitumor effect of AURKA is closely related to the degradation and activity of P53. MLN8054 is an ATP competitive AURKA inhibitor, and had completed phase I clinical trials in patients with advanced solid tumors [53]. Elevated expression of AURKA adversely affects prognosis in estrogen receptor (ER)–positive and HER2-negative and triple-negative breast cancer and is associated with resistance to taxanes. In this randomized clinical trial including 139 patients, the addition of oral MLN8237 to a reduced dose of weekly paclitaxel significantly improved progression-free survival compared with paclitaxel alone, and toxic effects with paclitaxel plus MLN8237 were manageable with MLN8237 dose reduction [54]. ENMD-2076 treatment resulted in partial response or clinical benefit lasting more than 6 months in 16.7% of patients with pretreated, advanced, or metastatic TNBC. Treatment with ENMD-2076 resulted in a decrease in cellular proliferation and microvessel density and an increase in p53 and p73 expression, consistent with preclinical observations [55].

AMG900 is an investigational, oral, selective pan-Aurora kinase inhibitor. AMG900 40 mg/day with granulocyte colony-stimulating factor had manageable toxicity and demonstrated single-agent activity in patients with heavily pretreated, chemotherapy-resistant ovarian cancer [56]. PF-03814735 is an oral ATP competitive inhibitor of AURKA and AURKB, and is generally well tolerated with manageable toxicities [57]. A phase II study has determined the efficacy and toxicity of PHA-739358 in patients with metastatic remover prostate cancer under two different intravenous regiments. PHA-739358 showed in vivo antitumor activity in a prostate cancer model and was well tolerated [58]. In 2019, AT9283 in children and adolescents with relapsed and refractory solid tumors was completed, but the results are to be announced. In 2019, Phase II Study of Curcumin vs Placebo for Chemotherapy-Treated Breast Cancer Patients Undergoing Radiotherapy. The primary outcome to be measured will be the change in NF-kB DNA binding (measured in peripheral blood mononuclear cells as ng/well) after 6 weeks of treatment with daily placebo or Meriva. NF-kB DNA binding and has

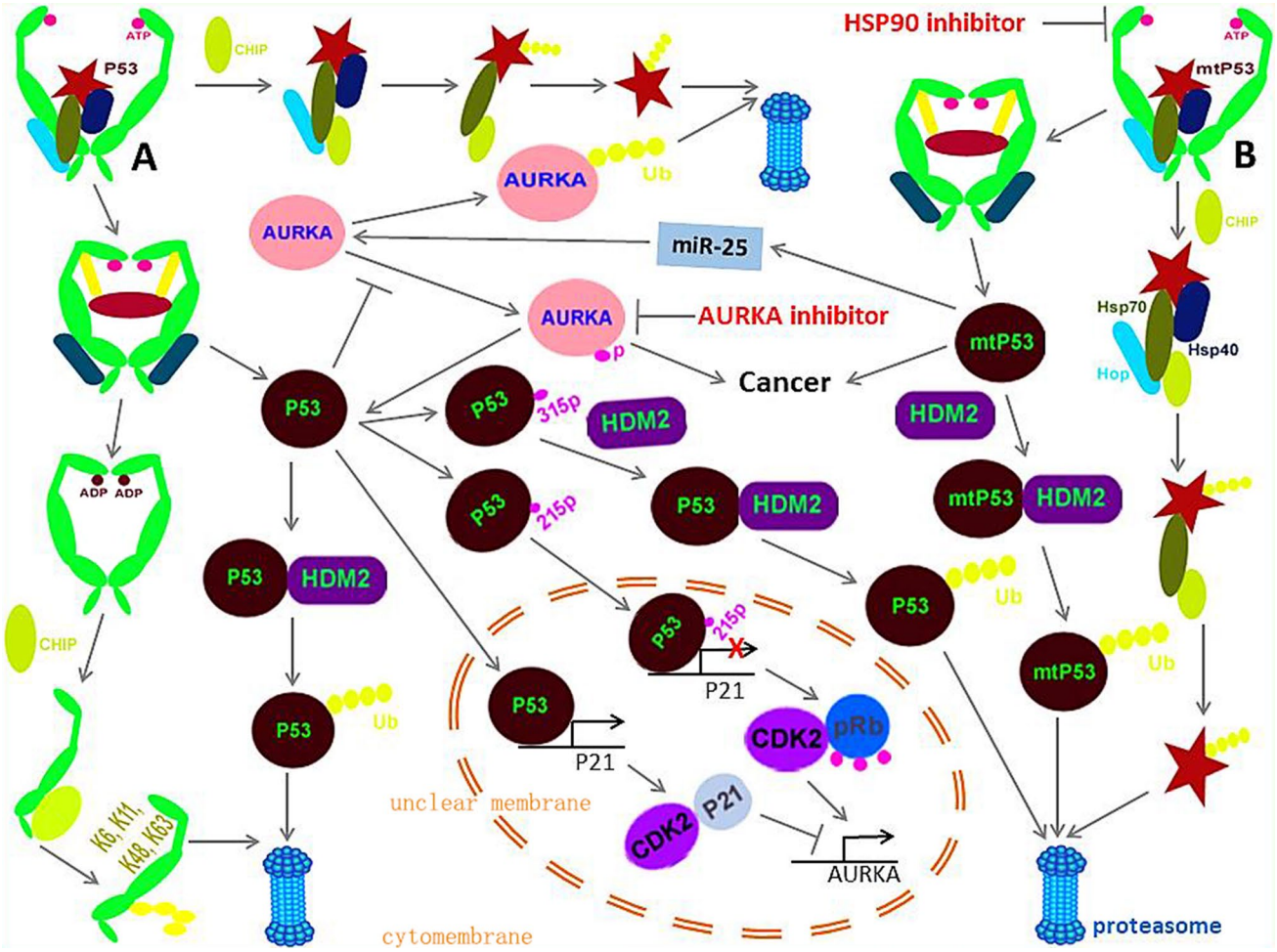

Fig. 2 Interrelation of HSP90, mtP53, P53, and AURKA. A. HSP90 chaperones with P53 in the cytoplasm. B. HSP90 chaperones with mtP53 in the cytoplasm

Table 1 Two categories of AURKA inhibitors for breast cancer from clinical trials

Inhibitors	Target	Method	Disease	Phase	References
MLN8054	AURKA	oral	Advanced solid tumors	I	[53]
MLN8237	AURKA	oral	Metastatic Breast Cancer	II	[54]
ENMD-2076	AURKA	oral	Triple negative breast cancer	II	[55]
AMG-900	Pan-Aurora	iv	Advanced solid tumors	I	[56]
PF-03814735	Pan-Aurora	oral	Advanced solid tumors	I	[57]
AT9283	Pan-Aurora	iv	Refractory solid tumors	I	–
Curcumin	Pan-Aurora	oral	Breast cancer	II	–

iv intraperitoneal injection

been associated with fatigue in breast cancer patients. The secondary outcome to be measured will be the change in plasma sTNFR2 (in pg/ml) after 6 weeks of treatment with daily placebo or Meriva. Plasma sTNFR2 is a downstream mediator of NF-kB DNA binding and has been associated with fatigue in breast cancer patients. Curcumin is derived from turmeric. Oral curcumin is well tolerated and, despite its limited absorption, has biological activity in some patients with pancreatic cancer [59]. The above AURKA inhibitors have shown therapeutic effects on cancer to varying degrees, so AURKA as a target to treat AURKA overexpression in breast cancer is expected to improve the treatment effect of breast cancer and solve the problem of chemotherapy resistance.

HSP90 inhibitors

HSP90 exists mainly in inactive form in normal somatic cells and in highly active form in cancer cells [60]. The significant advantage of HSP90 inhibitors is to simultaneously promote the degradation of multiple oncogenic proteins, thereby blocking multiple carcinogenic pathways. HSP90 inhibitors are divided into three categories based on their binding sites: NTD inhibitors, MD inhibitors, and CTD inhibitors. At present, most active HSP90 inhibitors are NTD inhibitors, including 17-AAG, IPI-504, 17-DMAG (Retaspimycin), STA-9090 (Ganetespib), and AUY922, while CTD inhibitors only found that BIIB021 has a good inhibitory effect on HSP90 [61]. According to their structural categories, HSP90 inhibitors are divided into three categories: Geldanamycin analoges, such as 17-AAG, IPI-504 and 17-DMAG; Resorcinol derivatives, such as STA-9090, AUY922; Purine analoges, like BIIB021. Some completed clinical studies of these HSP90 inhibitors are summarized in Table 2. Because 17-AAG inhibits signaling through the RAS/RAF/MEK/ERK and PI3K pathways, combining 17-AAG with carboplatin/paclitaxel can be beneficial in treating breast cancer. 17-AAG provides better anti-tumor activity and clinical efficiency when is combined with carboplatin/paclitaxel compared to when those agents are used alone. In addition, combining 17-AAG with antitumor agents can prevent the development of drug resistance in cancer treatment [62]. A multicenter trial evaluates IPI-504 plus trastuzumab in patients with advanced or metastatic HER2-positive breast cancer [63]. 17-DMAG as a semi-synthetic derivative of geldanamycin, has several advantages over 17-AAG such as higher water solubility, good bioavailability, reduced metabolism, and greater anti-tumor capability. 17-DMAG binds to HSP90 and inhibits its function, eventually leading to the degradation of HSP90 client protein [64]. STA-9090 (Ganetespib) is a HSP90 inhibitor with clinical benefit due to the clinical efficacy of metastatic breast cancer, but it has gastrointestinal toxicity [65]. NVP-AUY922 is an ATP competitive HSP90 inhibitor, and it potently inhibits growth in a variety of tumor xenografts in vivo and phase I of clinical study. Phase Ib/II study to determine the maximum tolerated dose of NVP-AUY922 in advanced solid malignancies, and efficacy in HER2 + or ER + locally advanced or metastatic breast cancer patients is under study. Schedule Finding of BIIB021 Plus Aromasin in hormone receptor positive metastatic breast cancer are not yet available. BIIB021 is an oral HSP90 inhibitor, which has a better affinity for HSP90 than 17-AAG, and may have better antitumor activity against resistant organs such as adrenal, brain, and testicular tumors [66]. HSP90 is highly expressed in a variety of cancers, so the combination of HSP90 and AURKA is better for the treatment of cancer with AURKA overexpression and TP53 mutations. Selection of HSP90 inhibitor will be the research direction and focus of cancer treatment.

Discussion

Some progress has been made in the treatment of breast cancer, but the recurrence and metastasis of breast cancer have become difficult to overcome. It is known that drug resistance is an important cause of breast cancer recurrence. The development of chemoresistance is a major hindrance to the effective treatment of cancer. Therefore, how to understand and circumvent the mutual resistance between treatments and improve the effect of combination therapy is a problem that needs to be solved urgently in clinical practice, and it is also a hot spot for basic research. A large number of solid tumors show AURKA overexpression and P53 mutations, and it is considered to be related to poor tumor treatment efficacy and drug resistance. AURKA overexpression is strongly associated with decreased survival and is an independent prognostic marker [67]. Abnormal expression of AURKA leads to functional defects of the centrosome and disturbance of the bipolar spindle, which leads to asymmetric separation of chromosomes during cleavage and induces chromosomal instability, thereby obtaining activation of oncogenes or inactivation of tumor suppressor genes. The aurora kinases are a family of serine-threonine kinases integral to mitotic cell division and have recently emerged as novel anti-cancer targets. Indeed, it is unlikely that such would be the case: a genomic analysis of 100 primary breast cancers suggested that single driver mutations were found

Table 2 Three categories of HSP90 inhibitors for breast cancer from clinical trials

Site	Structure class	Inhibitor	Tumor type	Phase	References
NTD	Geldanamycin analoges	17-AAG	Breast cancer	II	[62]
NTD	Geldanamycin analoges	IPI-504 + Trastuzumab	Breast cancer	II	[63]
NTD	Geldanamycin analoges	17-DMAG	Breast cancer	II	[64]
NTD	Resorcinol derivatives	STA-9090	Metastatic Breast Cancer	II	[65]
NTD	Resorcinol derivatives	NVP-AUY922 + Trastuzumab	Breast cancer	Ib/II	–
CTD	Purine analoges	BIIB021	Metastatic Breast Cancer	II	–

in only 28% of cases, and some cancers had as many as six driver mutations [68].

For TP53 mutations, there was an article presented data linking specific mutations in the TP53 gene to primary resistance to doxorubicin therapy and early relapse in breast cancer patients [42]. P53 mutation exacerbates host cell genome instability, increases the risk of cancer, and enhances the invasion and migration and resistance of cancer cells, which is an important reason for the poor prognosis of patients with P53 mutation tumors [45]. Due to too many types of P53 mutations, the design of drugs targeting mtP53 is difficult and the application is limited, so better alternative treatments need to be found. Research has shown that HSP90 is important for the stability and activity of mtP53 in vivo [16, 26]. Therefore, AURKA and HSP90 are very good targets for the treatment of breast cancer with AURKA overexpression and TP53 mutations. Moreover, compared with single drug therapy in the treatment of cancer, the combination of AURKA inhibitor and HSP90 inhibitor can reduce the side effects and drug resistance caused by overdose of a certain drug. Besides mtP53, HSP90 inhibitor can promote the degradation of many other oncogenic proteins. Because HSP90 inhibitor achieves "multi-point attack", it has a good effect in treating tumors [69]. In order to reduce the side effects of HSP90 inhibitor, we need to screen HSP90 inhibitor with minimal side effects and combine other drugs to reduce the dosage of HSP90 inhibitor.

Conclusion

In summary, the combination of AURKA inhibitor and HSP90 inhibitor to treat cancer with AURKA overexpression and TP53 mutations is a promising treatment strategy. This review describes the research status of AURKA and HSP90 in breast cancer, summarizes the structure, function, and the chaperone cycle of HSP90, elaborates the interrelation between HSP90, mtP53, P53, and AURKA, and proposes targeting HSP90 and AURKA to treat breast cancer with AURKA overexpression and TP53 mutations. Through this review, we hope to promote the research of HSP90, mtP53, P53, and AURKA, bring more good strategies for cancer treatment, solve the problem of drug resistance and improve the therapeutic effect of cancer.

Author contributions FW and QW contributed to conceptualization and writing, reviewing and editing of the manuscript. HZ, HT, BH, and TQ contributed to investigation.

Funding This research was supported by the National Natural Science Foundation of China (No. 22072005, 21773015) and the Natural Science Foundation of Beijing Municipality (No. 2202021).

Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.
2. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001;98(19):10869–74. https://doi.org/10.1073/pnas.191367098.
3. Diamond JR, Eckhardt SG, Tan AC, Newton TP, Selby HM, Brunkow KL, Kachaeva MI, Varella-Garcia M, Pitts TM, Bray MR, et al. Predictive biomarkers of sensitivity to the aurora and angiogenic kinase inhibitor ENMD-2076 in preclinical breast cancer models. Clin Cancer Res. 2013;19(1):291–303. https://doi.org/10.1158/1078-0432.CCR-12-1611.
4. Jalalirad M, Haddad TC, Salisbury JL, Radisky D, Zhang M, Schroeder M, Tuma A, Leof E, Carter JM, Degnim AC, et al. Aurora-A kinase oncogenic signaling mediates TGF-beta-induced triple-negative breast cancer plasticity and chemoresistance. Oncogene. 2021;40(14):2509–23. https://doi.org/10.1038/s41388-021-01711-x.
5. Zeichner SB, Terawaki H, Gogineni K. A review of systemic treatment in metastatic triple-negative breast cancer. Breast Cancer. 2016;10:25–36. https://doi.org/10.4137/BCBCR.S32783.
6. El Zein D, Hughes M, Kumar S, Peng X, Oyasiji T, Jabbour H, Khoury T. Metaplastic carcinoma of the breast is more aggressive than triple-negative breast cancer: a study from a single institution and review of literature. Clin Breast Cancer. 2017;17(5):382–91. https://doi.org/10.1016/j.clbc.2017.04.009.
7. Tray N, Taff J, Singh B, Suh J, Ngo N, Kwa M, Troxel AB, Chae YK, Kurzrock R, Patel SP, et al. Metaplastic breast cancers: genomic profiling, mutational burden and tumor-infiltrating lymphocytes. Breast. 2019;44:29–32. https://doi.org/10.1016/j.breast.2018.12.010.
8. Tray N, Taff J, Adams S. Therapeutic landscape of metaplastic breast cancer. Cancer Treat Rev. 2019;79:101888. https://doi.org/10.1016/j.ctrv.2019.08.004.
9. Sledge GW Jr. Curing metastatic breast cancer. J Oncol Pract. 2016;12(1):6–10. https://doi.org/10.1200/JOP.2015.008953.
10. Bertolin G, Tramier M. Insights into the non-mitotic functions of aurora kinase a: more than just cell division. Cell Mol Life Sci. 2020;77(6):1031–47. https://doi.org/10.1007/s00018-019-03310-2.
11. Tang A, Gao K, Chu L, Zhang R, Yang J, Zheng J. Aurora kinases: novel therapy targets in cancers. Oncotarget. 2017;8(14):23937–54. https://doi.org/10.18632/oncotarget.14893.
12. Tavernier N, Sicheri F, Pintard L. Aurora A kinase activation: different means to different ends. J Cell Biol. 2021;220(9):e202106128. https://doi.org/10.1083/jcb.202106128.
13. Cirak Y, Furuncuoglu Y, Yapicier O, Aksu A, Cubukcu E. Aurora A overexpression in breast cancer patients induces taxane resistance and results in worse prognosis. J BUON. 2015;20(6):1414–9.
14. Boos SL, Loevenich LP, Vosberg S, Engleitner T, Ollinger R, Kumbrink J, Rokavec M, Michl M, Greif PA, Jung A, et al. Disease modeling on tumor organoids implicates AURKA as a

therapeutic target in liver metastatic colorectal cancer. Cell Mol Gastroenterol Hepatol. 2021;13(2):517–40. https://doi.org/10.1016/j.jcmgh.2021.10.008.
15. Pick E, Kluger Y, Giltnane JM, Moeder C, Camp RL, Rimm DL, Kluger HM. High HSP90 expression is associated with decreased survival in breast cancer. Can Res. 2007;67(7):2932–7. https://doi.org/10.1158/0008-5472.CAN-06-4511.
16. Blagosklonny MV, Toretsky J, Bohen S, Neckers L. Mutant conformation of p53 translated in vitro or in vivo requires functional HSP90. Proc Natl Acad Sci USA. 1996;93(16):8379–83. https://doi.org/10.1073/pnas.93.16.8379.
17. Marei HE, Althani A, Afifi N, Hasan A, Caceci T, Pozzoli G, Morrione A, Giordano A, Cenciarelli C. p53 signaling in cancer progression and therapy. Cancer Cell Int. 2021;21(1):703. https://doi.org/10.1186/s12935-021-02396-8.
18. Liu Y, Tavana O, Gu W. p53 modifications: exquisite decorations of the powerful guardian. J Mol Cell Biol. 2019;11(7):564–77. https://doi.org/10.1093/jmcb/mjz060.
19. Hu J, Cao J, Topatana W, Juengpanich S, Li S, Zhang B, Shen J, Cai L, Cai X, Chen M. Targeting mutant p53 for cancer therapy: direct and indirect strategies. J Hematol Oncol. 2021;14(1):157. https://doi.org/10.1186/s13045-021-01169-0.
20. Ice RJ, McLaughlin SL, Livengood RH, Culp MV, Eddy ER, Ivanov AV, Pugacheva EN. NEDD9 depletion destabilizes Aurora A kinase and heightens the efficacy of Aurora A inhibitors: implications for treatment of metastatic solid tumors. Can Res. 2013;73(10):3168–80. https://doi.org/10.1158/0008-5472.CAN-12-4008.
21. Miralaei N, Majd A, Ghaedi K, Peymani M, Safaei M. Integrated pan-cancer of AURKA expression and drug sensitivity analysis reveals increased expression of AURKA is responsible for drug resistance. Cancer Med. 2021;10(18):6428–41. https://doi.org/10.1002/cam4.4161.
22. Yang H, He L, Kruk P, Nicosia SV, Cheng JQ. Aurora-A induces cell survival and chemoresistance by activation of Akt through a p53-dependent manner in ovarian cancer cells. Int J Cancer. 2006;119(10):2304–12. https://doi.org/10.1002/ijc.22154.
23. Li Y, Tang K, Zhang H, Zhang Y, Zhou W, Chen X. Function of Aurora kinase A in taxol-resistant breast cancer and its correlation with P-gp. Mol Med Rep. 2011;4(4):739–46. https://doi.org/10.3892/mmr.2011.494.
24. Yan M, Wang C, He B, Yang M, Tong M, Long Z, Liu B, Peng F, Xu L, Zhang Y, et al. Aurora-A kinase: a potent oncogene and target for cancer therapy. Med Res Rev. 2016;36(6):1036–79. https://doi.org/10.1002/med.21399.
25. Yang N, Wang C, Wang Z, Zona S, Lin SX, Wang X, Yan M, Zheng FM, Li SS, Xu B, et al. FOXM1 recruits nuclear aurora kinase A to participate in a positive feedback loop essential for the self-renewal of breast cancer stem cells. Oncogene. 2017;36(24):3428–40. https://doi.org/10.1038/onc.2016.490.
26. Birbo B, Madu EE, Madu CO, Jain A, Lu Y. Role of HSP90 in cancer. Int J Mol Sci. 2021;22(19):10317. https://doi.org/10.3390/ijms221910317.
27. Kim JY, Cho T-M, Park JM, Park S, Park M, Nam KD, Ko D, Seo J, Kim S, Jung E, et al. A novel HSP90 inhibitor SL-145 suppresses metastatic triple-negative breast cancer without triggering the heat shock response. Oncogene. 2022. https://doi.org/10.1038/s41388-022-02269-y.
28. Li D, Marchenko ND, Schulz R, Fischer V, Velasco-Hernandez T, Talos F, Moll UM. Functional inactivation of endogenous MDM2 and CHIP by HSP90 causes aberrant stabilization of mutant p53 in human cancer cells. Mol Cancer Res. 2011;9(5):577–88. https://doi.org/10.1158/1541-7786.MCR-10-0534.
29. Subramanian C, Grogan PT, Wang T, Bazzill J, Zuo A, White PT, Kalidindi A, Kuszynski D, Wang G, Blagg BSJ, et al. Novel C-terminal heat shock protein 90 inhibitors target breast cancer stem cells and block migration, self-renewal, and epithelial-mesenchymal transition. Mol Oncol. 2020;14(9):2058–68. https://doi.org/10.1002/1878-0261.12686.
30. Sumi MP, Ghosh A. Hsp90 in human diseases: molecular mechanisms to therapeutic approaches. Cells. 2022;11(6):976. https://doi.org/10.3390/cells11060976.
31. Biebl MM, Buchner J. Structure, function, and regulation of the Hsp90 machinery. Cold Spring Harb Perspect Biol. 2019;11(9):106–17. https://doi.org/10.1101/cshperspect.a034017.
32. Niu M, Zhang B, Li L, Su Z, Pu W, Zhao C, Wei L, Lian P, Lu R, Wang R, et al. Targeting HSP90 inhibits proliferation and induces apoptosis through AKT1/ERK pathway in lung cancer. Front Pharmacol. 2021;12:724192. https://doi.org/10.3389/fphar.2021.724192.
33. Dahiya V, Rutz DA, Moessmer P, Muhlhofer M, Lawatscheck J, Rief M, Buchner J. The switch from client holding to folding in the Hsp70/Hsp90 chaperone machineries is regulated by a direct interplay between co-chaperones. Mol Cell. 2022;82(8):1543-1556.e6. https://doi.org/10.1016/j.molcel.2022.01.016.
34. Gopal U, Bohonowych JE, Lema-Tome C, Liu A, Garrett-Mayer E, Wang B, Isaacs JS. A novel extracellular Hsp90 mediated co-receptor function for LRP1 regulates EphA2 dependent glioblastoma cell invasion. PLoS ONE. 2011;6(3):e17649. https://doi.org/10.1371/journal.pone.0017649.
35. Roe SM, Ali MM, Meyer P, Vaughan CK, Panaretou B, Piper PW, Prodromou C, Pearl LH. The Mechanism of Hsp90 regulation by the protein kinase-specific cochaperone p50(cdc37). Cell. 2004;116(1):87–98. https://doi.org/10.1016/s0092-8674(03)01027-4.
36. Radli M, Rüdiger SGD. Dancing with the diva: Hsp90–client interactions. J Mol Biol. 2018;430(18):3029–40. https://doi.org/10.1016/j.jmb.2018.05.026.
37. Li Z, Zhou L, Prodromou C, Savic V, Pearl LH. HECTD3 Mediates an HSP90-dependent degradation pathway for protein kinase clients. Cell Rep. 2017;19(12):2515–28. https://doi.org/10.1016/j.celrep.2017.05.078.
38. Sima S, Richter K. Regulation of the Hsp90 system. Biochim et Biophys Acta (BBA)—Mol Cell Res. 1865;6:889–97. https://doi.org/10.1016/j.bbamcr.2018.03.008.
39. Zhan S, Wang T, Ge W. Multiple functions of the E3 ubiquitin ligase CHIP in immunity. Int Rev Immunol. 2017;36(5):300–12. https://doi.org/10.1080/08830185.2017.1309528.
40. Alexandrova EM, Yallowitz AR, Li D, Xu S, Schulz R, Proia DA, Lozano G, Dobbelstein M, Moll UM. Improving survival by exploiting tumour dependence on stabilized mutant p53 for treatment. Nature. 2015;523(7560):352–6. https://doi.org/10.1038/nature14430.
41. Park SJ, Borin BN, Martinez-Yamout MA, Dyson HJ. The client protein p53 adopts a molten globule-like state in the presence of Hsp90. Nat Struct Mol Biol. 2011;18(5):537–41. https://doi.org/10.1038/nsmb.2045.
42. Schulz-Heddergott R, Moll UM. Gain-of-function (GOF) mutant p53 as actionable therapeutic target. Cancers. 2018;10(6):188. https://doi.org/10.3390/cancers10060188.
43. Peng Y, Chen L, Li C, Lu W, Chen J. Inhibition of MDM2 by hsp90 contributes to mutant p53 stabilization. J Biol Chem. 2001;276(44):40583–90. https://doi.org/10.1074/jbc.M102817200.
44. Calderwood SK, Gong J. Heat shock proteins promote cancer: it's a protection racket. Trends Biochem Sci. 2016;41(4):311–23. https://doi.org/10.1016/j.tibs.2016.01.003.
45. Sabapathy K, Lane DP. Therapeutic targeting of p53: all mutants are equal, but some mutants are more equal than others. Nat Rev Clin Oncol. 2018;15(1):13–30. https://doi.org/10.1038/nrclinonc.2017.151.

46. Kundrat L, Regan L. Identification of residues on Hsp70 and Hsp90 ubiquitinated by the cochaperone CHIP. J Mol Biol. 2010;395(3):587–94. https://doi.org/10.1016/j.jmb.2009.11.017.
47. Katayama H, Sasai K, Kawai H, Yuan ZM, Bondaruk J, Suzuki F, Fujii S, Arlinghaus RB, Czerniak BA, Sen S. Phosphorylation by aurora kinase A induces Mdm2-mediated destabilization and inhibition of p53. Nat Genet. 2004;36(1):55–62. https://doi.org/10.1038/ng1279.
48. Liu Q, Kaneko S, Yang L, Feldman RI, Nicosia SV, Chen J, Cheng JQ. Aurora-A abrogation of p53 DNA binding and transactivation activity by phosphorylation of serine 215. J Biol Chem. 2004;279(50):52175–82. https://doi.org/10.1074/jbc.M406802200.
49. Hsueh KW, Fu SL, Chang CB, Chang YL, Lin CH. A novel Aurora-A-mediated phosphorylation of p53 inhibits its interaction with MDM2. Biochem Biophys Acta. 2013;1834(2):508–15. https://doi.org/10.1016/j.bbapap.2012.11.005.
50. Wu CC, Yang TY, Yu CT, Phan L, Ivan C, Sood AK, Hsu SL, Lee MH. p53 negatively regulates Aurora A via both transcriptional and posttranslational regulation. Cell Cycle. 2012;11(18):3433–42. https://doi.org/10.4161/cc.21732.
51. Mao JH, Wu D, Perez-Losada J, Jiang T, Li Q, Neve RM, Gray JW, Cai WW, Balmain A. Crosstalk between aurora-A and p53: frequent deletion or downregulation of aurora-A in tumors from p53 null mice. Cancer Cell. 2007;11(2):161–73. https://doi.org/10.1016/j.ccr.2006.11.025.
52. Li Z, Sun Y, Chen X, Squires J, Nowroozizadeh B, Liang C, Huang J. p53 Mutation directs AURKA overexpression via miR-25 and FBXW7 in prostatic small cell neuroendocrine carcinoma. Mol Cancer Res. 2015;13(3):584–91. https://doi.org/10.1158/1541-7786.MCR-14-0277-T.
53. Dees EC, Infante JR, Cohen RB, O'Neil BH, Jones S, von Mehren M, Danaee H, Lee Y, Ecsedy J, Manfredi M, et al. Phase 1 study of MLN8054, a selective inhibitor of aurora A kinase in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2011;67(4):945–54. https://doi.org/10.1007/s00280-010-1377-y.
54. O'Shaughnessy J, McIntyre K, Wilks S, Ma L, Block M, Andorsky D, Danso M, Locke T, Scales A, Wang Y. Efficacy and safety of weekly paclitaxel with or without oral alisertib in patients with metastatic breast cancer: a randomized clinical trial. JAMA Netw Open. 2021;4(4):e214103. https://doi.org/10.1001/jamanetworkopen.2021.4103.
55. Diamond JR, Eckhardt SG, Pitts TM, van Bokhoven A, Aisner D, Gustafson DL, Capasso A, Sams S, Kabos P, Zolman K, et al. A phase II clinical trial of the aurora and angiogenic kinase inhibitor ENMD-2076 for previously treated, advanced, or metastatic triple-negative breast cancer. Breast Cancer Res: BCR. 2018;20(1):82. https://doi.org/10.1186/s13058-018-1014-y.
56. Carducci M, Shaheen M, Markman B, Hurvitz S, Mahadevan D, Kotasek D, Goodman OB Jr, Rasmussen E, Chow V, Juan G, et al. A phase 1, first-in-human study of AMG 900, an orally administered pan-Aurora kinase inhibitor, in adult patients with advanced solid tumors. Invest New Drugs. 2018;36(6):1060–71. https://doi.org/10.1007/s10637-018-0625-6.
57. Schoffski P, Jones SF, Dumez H, Infante JR, Van Mieghem E, Fowst C, Gerletti P, Xu H, Jakubczak JL, English PA, et al. Phase I, open-label, multicentre, dose-escalation, pharmacokinetic and pharmacodynamic trial of the oral aurora kinase inhibitor PF-03814735 in advanced solid tumours. Eur J Cancer. 2011;47(15):2256–64. https://doi.org/10.1016/j.ejca.2011.07.008.
58. Meulenbeld HJ, Bleuse JP, Vinci EM, Raymond E, Vitali G, Santoro A, Dogliotti L, Berardi R, Cappuzzo F, Tagawa ST, et al. Randomized phase II study of danusertib in patients with metastatic castration-resistant prostate cancer after docetaxel failure. BJU Int. 2013;111(1):44–52. https://doi.org/10.1111/j.1464-410X.2012.11404.x.
59. Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL, Ng CS, Badmaev V, Kurzrock R. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clinical Cancer Res. 2008;14(14):4491–9. https://doi.org/10.1158/1078-0432.CCR-08-0024.
60. Kamal A, Thao L, Sensintaffar J, Zhang L, Boehm MF, Fritz LC, Burrows FJ. A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors. Nature. 2003;425(6956):407–10. https://doi.org/10.1038/nature01913.
61. He W, Hu H. BIIB021, an Hsp90 inhibitor: a promising therapeutic strategy for blood malignancies (Review). Oncol Rep. 2018;40(1):3–15. https://doi.org/10.3892/or.2018.6422.
62. Gartner EM, Silverman P, Simon M, Flaherty L, Abrams J, Ivy P, Lorusso PM. A phase II study of 17-allylamino-17-demethoxygeldanamycin in metastatic or locally advanced, unresectable breast cancer. Breast Cancer Res Treat. 2012;131(3):933–7. https://doi.org/10.1007/s10549-011-1866-7.
63. Modi S, Saura C, Henderson C, Lin NU, Mahtani R, Goddard J, Rodenas E, Hudis C, O'Shaughnessy J, Baselga J. A multicenter trial evaluating retaspimycin HCL (IPI-504) plus trastuzumab in patients with advanced or metastatic HER2-positive breast cancer. Breast Cancer Res Treat. 2013;139(1):107–13. https://doi.org/10.1007/s10549-013-2510-5.
64. Mellatyar H, Talaei S, Pilehvar-Soltanahmadi Y, Barzegar A, Akbarzadeh A, Shahabi A, Barekati-Mowahed M, Zarghami N. Targeted cancer therapy through 17-DMAG as an Hsp90 inhibitor: overview and current state of the art. Biomed Pharmacother = Biomedecine & pharmacotherapie. 2018;102:608–17. https://doi.org/10.1016/j.biopha.2018.03.102.
65. Jhaveri K, Chandarlapaty S, Lake D, Gilewski T, Robson M, Goldfarb S, Drullinsky P, Sugarman S, Wasserheit-Leiblich C, Fasano J, et al. A phase II open-label study of ganetespib, a novel heat shock protein 90 inhibitor for patients with metastatic breast cancer. Clin Breast Cancer. 2014;14(3):154–60. https://doi.org/10.1016/j.clbc.2013.12.012.
66. Zhang H, Neely L, Lundgren K, Yang Y-C, Lough R, Timple N, Burrows F. BIIB021, a synthetic HSP90 inhibitor, has broad application against tumors with acquired multidrug resistance. Int J Cancer. 2009;126(5):1226–34. https://doi.org/10.1002/ijc.24825.
67. Du R, Huang C, Liu K, Li X, Dong Z. Targeting AURKA in cancer: molecular mechanisms and opportunities for cancer therapy. Mol Cancer. 2021;20(1):15. https://doi.org/10.1186/s12943-020-01305-3.
68. Stephens PJ, Tarpey PS, Davies H, Van Loo P, Greenman C, Wedge DC, Nik-Zainal S, Martin S, Varela I, Bignell GR, et al. The landscape of cancer genes and mutational processes in breast cancer. Nature. 2012;486(7403):400–4. https://doi.org/10.1038/nature11017.
69. Zavareh RB, Spangenberg SH, Woods A, Martinez-Pena F, Lairson LL. HSP90 inhibition enhances cancer immunotherapy by modulating the surface expression of multiple immune checkpoint proteins. Cell Chem Biol. 2021;28(2):158–16155. https://doi.org/10.1016/j.chembiol.2020.10.005.