Molecular mechanism and targeted therapy of Hsp90 involved in lung cancer: New discoveries and developments (Review)

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Abstract. The exploration of the molecular mechanisms and signaling pathways on lung cancer is very important for developing new strategies of diagnosis and treatment to this disease, such as finding valuable lung cancer markers and molecularly targeted therapies. Previously, a number of studies disclose that heat shock protein 90 (Hsp90) is upregulated in cancer cells, tissues and serum of lung cancer patients, and its upregulation intimately correlates with the occurrence, development and outcome of lung cancer. On the contrary, inhibition of Hsp90 can suppress cell proliferation, motility and metastasis of lung cancer and promote apoptosis of lung cancer cells via complex signaling pathways. In addition, a series of Hsp90 inhibitors have been investigated as effective molecular targeted therapy tactics fighting against lung cancer. This review, systematically summarizes the role of Hsp90 in lung cancer, the molecular mechanisms and development of anti-Hsp90 treatment in lung cancer.

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1. Introduction

With the development of tumor molecular biology, progress of the detection and treatment of cancer has led to an impressive reduction in both mortality and morbidity. However, cancer still remains one of the most clinically challenging diseases (1). Today, it is believed that systemic chemotherapy improves the survival and quality of life of patients with advanced stage cancer, and improved the outcome of first-line therapy for advanced and metastatic cancer have primarily focused on the addition of targeted agents to platinum-based two-drug regimens (2). Medical studies suggest that understanding the molecular mechanism of tumors is critical for improving the diagnosis and treatment. Especially, the level of certain protein expression is associated with the prognosis and treatment of malignant tumors (3). Heat shock protein 90 (Hsp90) accounts for 1-2% of the amounts of cellular proteins under non-stressed conditions. However, it contents would go up approximately twice during environmental stress (4). Hsp90 performs a series of biological functions via complicated signals regulation by combining and disaggregation of ATP, and various client proteins and co-chaperones of Hsp90 are implicated in this process (5). Human Hsp90 includes four isoforms: Hsp90α and β (cytosolic isoforms), TRAP1 (in mitochondria) and Grp94 (in endoplasmic reticulum) (6). Hsp90β (Hsp90AB1) is regarded as a constitutive expression while Hsp90α (Hsp90AA1) as an inducible expression, it is proved that they have 86% amino acid sequence identity (7). Hsp90 has been found as a critical regulator of cell proliferation, development, mobility and metastasis in malignant tumors, which facilitates maturation and activation of oncogenic proteins, including many kinases and transcription regulatory factors (8). Also, Hsp90 exerts anti-apoptotic activity and affects growth processes tumor cells, and overexpression of Hsp90 has been obviously associated with drug resistance

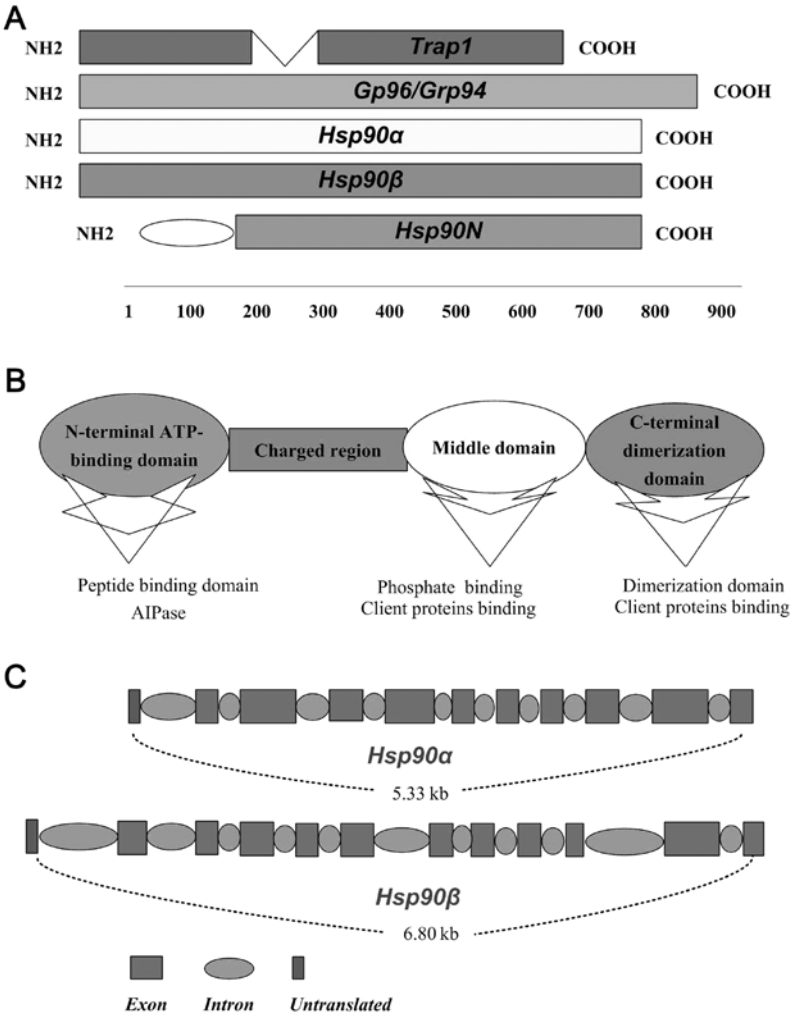

Figure 1. Molecular structure and function domain of Hsp90. (A) Hsp90α, Hsp90β, gp96 and the TRAP1 are four members of Hsp90 family 4. (B) Each protomer of Hsp90 comprises three regions, ATP-binding domain (N-domain), middle domain (M-do-main), and C-terminal dimerization domain (C-do-main); the 25-kDa N-terminal of Hsp90 is relatively conserved, which is linked with 55 kDa C-terminal domains by a charged linker region; the N-terminal domain of Hsp90 combined with ATP is intimately tied up with a middle domain via an unstructured charged linker, and the C-terminal domain; the middle domain of Hsp90 is ~35 kDa, and a binding site for client proteins and nuclear localization signal, which is implicated in recognising of collaborating proteins and adjusting the activation molecular chaperones. (C) Hsp90α and Hsp90β, exist as a result of the duplication of the original gene and share 86% homology; the chromosome 14q32.33 encodes the Hsp90α, while Hsp90β is located at 6p21. Hsp90-coding genes include intron sequences and the second exon is the region of translational initiation of both Hsp90α and Hsp90β. Hsp90, heat shock protein 90; TRAP1, TNF receptor associated protein 1; ATP, adenosine-triphosphate.

and survival time of tumor patients (9). Previous studies show that Hsp90 is highly expressed in specimens of lung cancer and are associated with poor post-surgical survival time and lymphatic metastasis of lung cancer patients (10-13) indicating that upregulation of Hsp90 potentially facilitates proliferation and metastasis of lung cancer. However, anti-Hsp90 (Hsp90 inhibitors) studies have demonstrated that downregulation and function disruption of Hsp90 inhibits cell proliferation, motility and metastasis, and induces apoptosis of lung cancer cells (11,12,14). Here, we reviewed new findings on the role of Hsp90 in lung cancer, including the mechanisms and signaling pathways, the pre-clinical results of Hsp90 inhibition (14).

2. Molecular structure and function domain of Hsp90

As a homodimeric protein of ~90 kDa, Hsp90 performs complicated biological functions reacting with many collaborating proteins (co-chaperons and clients proteins of Hsp90) (15). As shown in Fig. 1A, Hsp90α, Hsp90β, gp96 and the TRAP1 are four members of Hsp90 family (7). Different members of Hsp90 family present the same action pattern but binding to specially appointed clients proteins, which depends in part on their locations and distribution within the different cells (16). Each protomer of Hsp90 comprises three regions, ATP-binding domain (N-domain), middle domain (M-domain), and C-terminal dimerization domain (C-domain) (17) (Fig. 1B). Constructively, the 25-kDa N-terminal of Hsp90 is relatively conserved, which is linked with 55 kDa C-terminal domains by a charged linker region and middle domain (16) (Fig. 1B). The middle domain of Hsp90 is ~35 kDa, has been investigated as a binding site for client proteins and nuclear localization signal, which is implicated in recognising of collaborating proteins and adjusting the activation molecular chaperones (18) (Fig. 1B). Hsp90 exerts relevant functions via binding and hydrolysis of ATP like a molecular clamp, which facilitates the combining and dissociation of its client proteins (19) (Fig. 1B). The important two members of Hsp90, Hsp90α and Hsp90β, exist as a result of the duplication of the

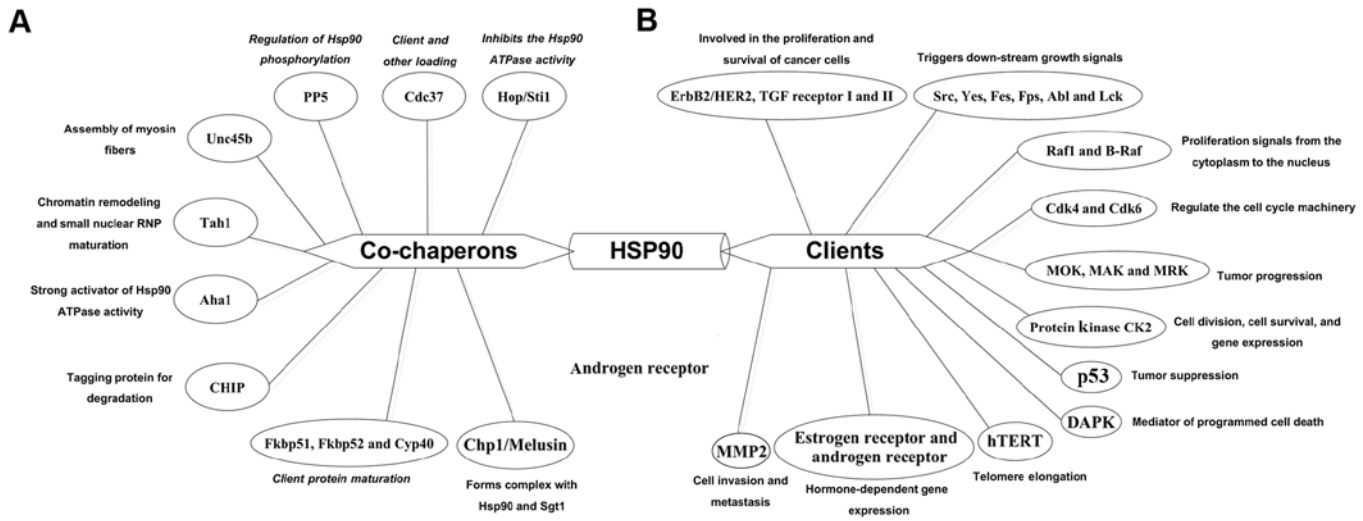

Figure 2. Co-chaperons and client proteins of Hsp90. (A) More than 20 different proteins regulate the activity and function of Hsp90, which are known as co-chaperones and these proteins regulate the chaperoning function of Hsp90 by activating and inhibiting the activity of Hsp90 ATPase and sometimes by recruiting the specific client proteins; some key co-chaperones include Hop/Sti1, Cdc37, p23/Sba1, PP5, Fkbp51, Fkbp52, Cyp40, Unc45b, Tah1, Aha1 and CHIP. (B) The specific co-chaperones of Hsp90 could have a specific intimate relationship with one, even more than one client protein and participate in a series of specific biological reactions; some key co-chaperones include ErbB2/HER2, IGF-I and TGF receptor I and II; the members of Src family, Yes, Fes, Fps, Abl and Lck; ERK1, ERK2, Raf1, B-Raf, Cdk4, Cdk6, hTERT, MMP2, p53, CK2, MOK, MAK, MRK, DAPK. Hsp90, heat shock protein 90; ATPase, adenylpyrophosphatase; Hop/Sti1, a co-chaperone adaptor protein for Hsp90; Cdc37, cell division cycle 37; p23/Sba1, the protein encoded by the PTGES3 gene; PP5, protein phosphatase 5; Fkbp51 and Fkbp52, Hsp90-associated human peptidyl prolyl *cis/trans* isomerases; Cyp40, cyclophilin 40; Unc45b, unc45 myosin chaperone b; Tah1, TPR7-containing protein associated with Hsp90; Aha1, activator of Hsp90 ATPase; CHIP, carboxyl-terminus of the Hsp70 interacting protein; ErbB2/HER2, human epidermal growth factor receptor-2; IGF-I, insulin-like growth factor 1; TGF, transforming growth factor; Yes, Fes, Fps, Abl and Lck, some of Src family tyrosine kinases; ERK, extracellular-signal-regulated kinase; Raf, rapidly accelerated fibrosarcoma gene; Cdk, cyclin-dependent kinase; hTERT, human telomerase reverse transcriptase; MMP2, matrix metalloproteinase-2; p53, tumor suppressor p53; CK2, casein kinase 2; MOK, MAK and MRK, MAPK-related protein kinases; DAPK, death associated protein kinase.

original gene and share 86% homology (20). In humans, the chromosome 14q32.33 encodes the Hsp90α, while Hsp90β is located at 6p21. Hsp90-coding genes include intron sequences and the second exon is the region of translational initiation of both Hsp90α and Hsp90β (7) (Fig. 1C).

3. Co-chaperons and client proteins of Hsp90

Co-chaperons of Hsp90. The discovery and structural characterization of the ATP-binding site in the N-terminal domain of HSP90, made it possible to determine the degree to which the ATPase activity of HSP90 contributed to the essential biological functions of HSP90 as a molecular chaperone. There are more than 20 different proteins that regulate the activity and function of Hsp90, which are known as co-chaperones (Fig. 2A). Of them, Hop/Sti1 inhibits the activity of Hsp90 ATPase and recruits steroid hormone receptor to Hsp90 (21,22). Cdc37 helps the loading of other co-chaperones of Hsp90 (18), p23/Sba1 inhibits the ATPase activity of Hsp90 and also promotes the maturation of client proteins (22,23). PP5 stabilises the status of Hsp90 phosphorylation promoting the efficient processing of client proteins (24,25). Human peptidyl prolyl *cis/trans* isomerases, Fkbp51, Fkbp52 and Cyp40 improve the client protein maturation of Hsp90 (26). Unc45b forms a stable complex with Hsp90 and selectively combines the myosin motor domain, and promotes motor domain folding (27). Together with the Tah1 cofactor, Hsp90 stabilize Pih1/Nop17 and increases the chromatin remodeling and small nuclear ribonucleoprotein maturation (28). Aha1 induces Hsp90 rearrangements that speeds up the conformational cycle, which defines a controlled progression through distinct intermediates (29). Co-chaperones of Hsp90 are also involved in other physiological processes, such as mitochondrial/chloroplast protein import, nuclear migration and melanoma progression (30).

Client proteins of Hsp90. The client proteins of Hsp90 have been found to be related to a wide aspects of physiological procedures including the regulation of cell cycle, communication of cell signals and regulation of cell transcription and post-transcriptional adjustment (Fig. 2B). Hsp90 plays a critical role in the function and stability of ErbB2/HER2 by binding to IGF-I and TGF receptor I and II (18,31,32). The members of Src family, Yes, Fes, Fps, Abl and Lck, have been shown to be related to the exertion of Hsp90 function, which activate the cascade reaction of downstream molecules (18,33,34). Two proteins of MAPK pathway, ERK1 and ERK2 regulate the growth of cells by phosphorylating many kinds of substrates within the nucleus. In addition, Hsp90 correlates with the structure and function of Raf-1 and B-Raf by interacting with Cdc37 (18,35,36). Clearly, the activity of CK2 depends upon the appearance of Hsp90 (12,37), estrogen and androgen receptors, require the assistance of Hsp90 to enable the steroid hormone ligand to bind (16). Inhibiting Hsp90 results in the proteolysis of hTERT, which affects the function of hTERT (38,39). Downregulation of Hsp90 reduces the expression of MMP9 and protects the MMP2 from degradation in malignant cells (40,41). Also, p53 interacts with Hsp90 in a relatively folded state, which may be chalked up to the destabilization by Hsp90 (42,43). Some Hsp90 client proteins,

Table I. Hsp90 expression in human lung cancer and correlation with clinical outcome.

Authors/Refs.	Lung cancer classification	Cell lines	Tissue	Blood	Techniques	Notes
Biaoxue Rong *et al* (10)	Lung cancer	Yes	Yes	No	IHC, WB	The upregulation of Hsp90β is associated with poor post-surgical survival time and lymphatic metastasis of lung cancer patients
Rong *et al* (13)	Lung cancer	No	Yes	Yes	IHC, ELISA	Upregulation of serum Hsp90β is associated with pathological grade and clinical stage of lung cancer patients
Su *et al* (46)	NSCLC	No	Yes	No	IHC	Nuclear accumulation of Hsp90 might be a predictor of metastasis and survival in patients with NSCLC
Gallegos *et al* (47)	NSCLC	Yes	Yes	No	Genomic hybridization	The survival patients whose tumors have low expression levels of Hsp90 is also longer and low Hsp90 expression to be related with longer overall survival
Liu *et al* (48)	NSCLC	No	Yes	No	PPA	Overexpression of Hsp90 in NSCLC correlates with a favorable overall survival in all NSCLC patients
Gomez-Casal *et al* (49)	NSCLC	Yes	No	No	IHC, WB, qRT-PCR	Hsp90 protein is present at high levels in parental T2821 and T2851 cells as well as in radioresistant T2821/R and T2851/R cells of lung cancer
Senju *et al* (51)	Lung cancer	Yes	Yes	No	IHC,WB, qRT-PCR	Remarkable high expression of Hsp90 protein in lung cancer cell lines and a more intense signal for Hsp90 by IHC in males, patients with smoking index over 600, and squamous cell carcinoma are observed
Wu *et al* (52)	NSCLC	No	Yes	No	IHC, WB	Hsp90-β protein is overexpressed in lung adenocarcinoma tumor tissues and correlates with poor outcomes in early stage ADC patients and low pathological grade tumors
Wang *et al* (53)	NSCLC	No	Yes	No	IHC	Hsp90β protein is overexpressed in NSCLC tissues, and is associated with lung cancer pathological type and overall survival in lung adenocarcinoma patients
Shi *et al* (54)	NSCLC	No	No	Yes	ELISA	Plasma Hsp90α protein levels are useful as a diagnostic biomarker in lung cancer and predict the responses of patients with lung cancer to chemotherapy

ADC, adenocarcinoma; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; ISH, *in situ* hybridization; NSCLC, non-small cell lung cancer; PPA, protein pathway array; qRT-PCR, real-time quantity PCR; WB, western blotting.

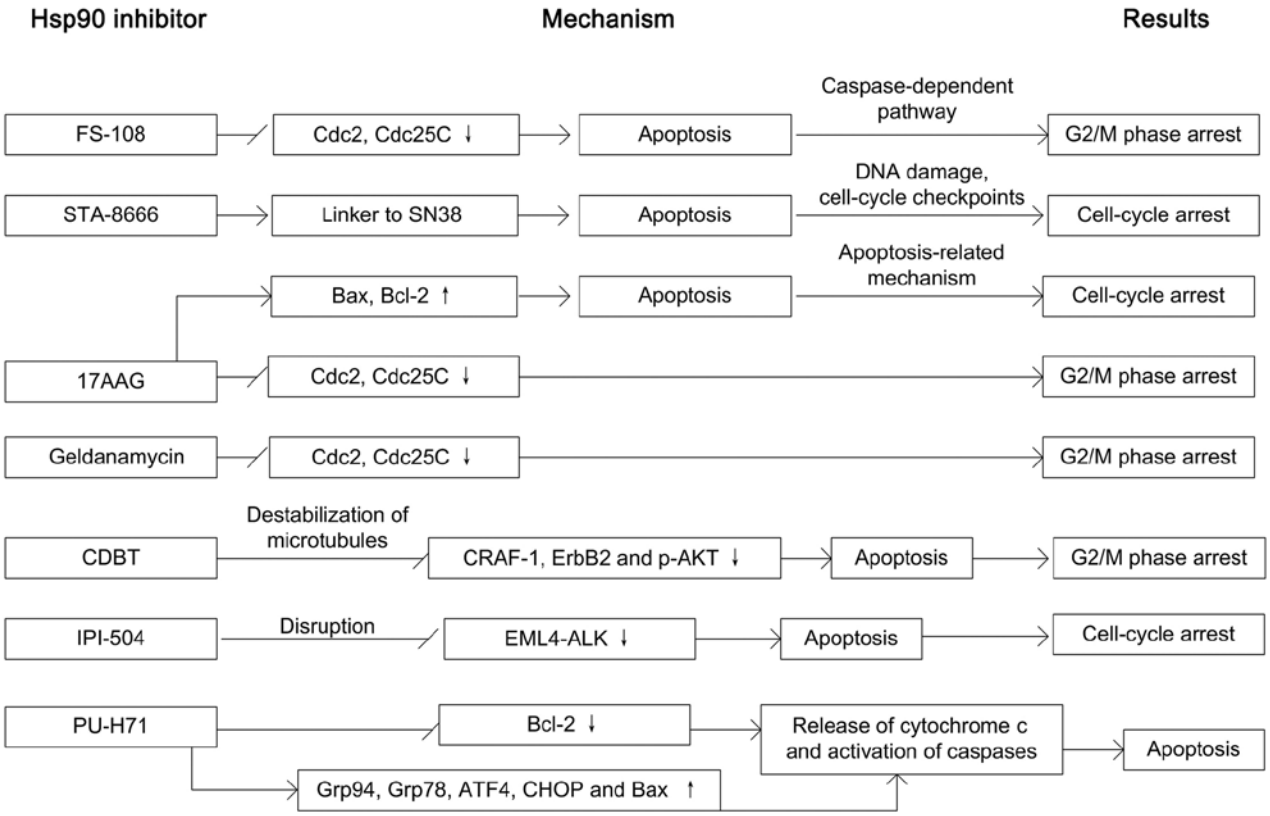

Figure 3. Influence of Hsp90 on the cell cycle regulation and cell apoptosis. Inhibition of Hsp90 induces G2/M phase arrest of lung cancer cells by reducing the expression of Cdc2 and Cdc25C and promotes apoptosis via a caspase-dependent pathway; inhibition of Hsp90 induces an effective cell cycle arrest, which is associated with DNA damage and cell cycle checkpoints, and apoptosis by regulating the expression of Bax and Bcl-2. Inhibition of Hsp90 causes the destabilization of microtubules and degradation of CRAF-1 and ERBB2 and phosphorylated AKT, leading to cell cycle arrest at the G2/M phase and reinforcement of apoptosis. Hsp90 inhibition leads to disruption of EML4-ALK and induces growth arrest and apoptosis in lung cancer cells. Hsp90 inhibition upregulates Grp94, Grp78, ATF4 and CHOP and induces apoptosis of lung cancer cells by downregulation of Bcl-2, upregulation of Bax, release of cytochrome *c* and activation of caspases. Hsp90, heat shock protein 90; Cdc2, cell division cycle 2; Cdc25C, cell division cycle 25C; DNA, deoxyribonucleic acid; Bax, bcl-2-like protein 4; Bcl-2, B-cell lymphoma-2; CRAF-1, threonine protein kinase; ERBB2, human epidermal growth factor receptor-2; AKT, anaplastic lymphoma kinase; EML4-ALK, echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase; Grp94, glucose-regulated protein 94; Grp78, glucose-regulated protein 78; ATF4, anti-activating transcription factor 4; CHOP, nuclear transcription factor.

including RAF, ErbB2, EGFR, MAK and hTERT, have been found to interact with Hsp90 and play important roles in the development of lung cancer (44,45).

4. Expression of Hsp90 in lung cancer

Table I lists the recent important findings on the expression of Hsp90 in lung cancer. Hsp90 is highly expressed in NSCLC patients, and increased Hsp90 positively correlates with age, lung squamous cell carcinoma (LSCC), ever-smoking history and metastasis of lymph node (46). Also, overexpression of Hsp90 in NSCLC patients relates with shorter overall survival (47), suggesting that it could be used to predict survival (48). In parental T2821 and T2851 cells of lung cancer, the protein expression of Hsp90 is upregulated, and in radioresistant T2821/R and T2851/R cells lines this phenomena is eminent and intimately correlates with the radioresistance of T2821/R and T2851/R cells (49). Compared with the control cells, the expression of Hsp90 in SPCA-1 and H446 cell lines of lung cancer is upregulated remarkably, which presents a dose-dependent pattern to geranylgeranylacetone (50). High expression of Hsp90 is also associated with male patients, patients with smoking index over 600, and SCLC (51). One study reports that overall survival (OS) of high-Hsp90β expression lung cancer is shorter than that of low-Hsp90β group and Hsp90β is an independent prognostic factor (11). In addition, overexpression of Hsp90β is found in tissues of lung adenocarcinoma, which is related to the poorly differentiated grade, shorten OS (52) and lymphatic invasion (10). Increased serum Hsp90β correlates with the differentiated grade and advanced clinical stage of patients with lung cancer, and assists the diagnosis and prognosis estimation (13). In one comparative study, Hsp90β in lung cancer tissues showed a higher expression than that in normal lung tissue and Hsp90β presents a higher expression in LAC tissues than in LSCC, and correlates with the poor survival of LAC patients (53). A study with a total of 2,247 individuals demonstrates that the plasma Hsp90α of lung cancer patients has a significantly higher level and correlates with advanced stage of lung cancer patients (stage III-IV) (54).

Currently, there are still some limitations on investigating the expression of Hsp90 in lung cancer. First, we still lack large number of samples and multiple center research. There is no high quality research concerning the expression of Hsp90 in lung tissues, blood, BALF, and malignant pleural effusion (MPE). Second, previous studies do not focus on Hsp90 gene

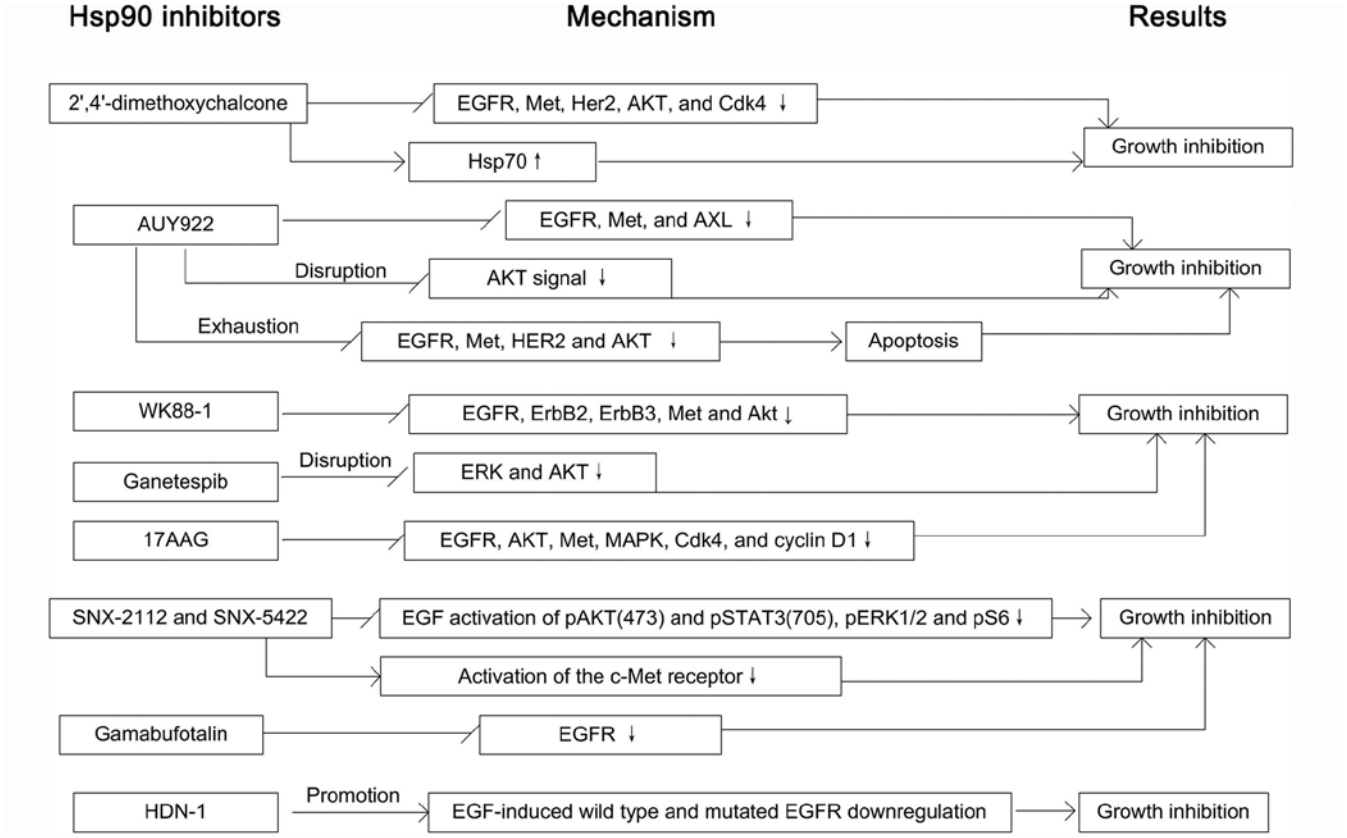

Figure 4. Influence of Hsp90 on the growth of lung cancer via EGFR signaling pathways. Hsp90 inhibition decreases the growth of NSCLC cells by downregulating EGFR, Met, Her2, Akt, and Cdk4, and upregulating Hsp70, and inhibits the proliferation and induces cell death by downregulation of EGFR and AXL. Hsp90 inhibition results in exhaustion of EGFR, Met, HER2 and AKT, which leads to the reinforcement of apoptosis; Hsp90 inhibition reduces the lung cancer cell survival via reducing the expression of EGFR, ErbB2, ErbB3, Met and Akt. Hsp90 inhibition and erlotinib stabilizes the expression state of EGFR inactivation and disrupts ERK and AKT signaling activity, which is associated with downregulation of EGFR and Met. Inhibition of Hsp90 exhausts EGFR, AKT, MAPK, Cdk4, and cyclin D1 and suppresses EGF activation of pAKT(473) and pSTAT3(705), pERK1/2 and pS6 and causes c-Met degradation; suppression of Hsp90 reduces expression of Hsp90-dependent client protein EGFR and results in a potential conformational change and degrades multiple oncoproteins and promotes EGF-induced wild-type and mutated EGFR downregulation. Hsp90, heat shock protein 90; EGFR, epidermal growth factor receptor; CDK4, cyclin-dependent kinase 4; ERBB, human epidermal growth factor receptor; AKT, anaplastic lymphoma kinase; Met, Met gene; Her2, human epidermal growth factor receptor-2; AXL, receptor tyrosine kinase; ERK, extracellular-signal-regulated kinase; MAPK, mitogen-activated protein kinase; EGF, epidermal growth factor; STAT3, signal transducer and activator of transcription 3; c-Met, proto-oncogene.

mutations and abnormal copy. Because a great deal of studies on inhibitors of Hsp90 that fight against lung cancer show that not all lung cancer respond with definite efficacy to inhibitors of Hsp90.

5. Biological functions of Hsp90 in lung cancer

From 2000 to now, investigating the relation between Hsp90 and lung cancer has become a very active field, especially on the efficacy of Hsp90 inhibitors that fight against lung cancer. It seems that different Hsp90 inhibitors affect different signaling pathways via specific signal molecules in development of lung cancer.

Influence of Hsp90 on cell cycle regulation and cell apoptosis of lung cancer. As shown in Fig. 3, Hsp90 inhibitor FS-108 induces G2/M phase arrest of gefitinib-resistant lung cancer cells by reducing the expression of Cdc2 and Cdc25C, and promotes apoptosis of gefitinib-resistant cells via a caspase-dependent pathway (55). STA-8666 combines a chemical moiety targeting active Hsp90 fused via cleavable linker to the active metabolite of irinotecan (SN38), and induces cell cycle arrest, associating with DNA damage and cell cycle checkpoints, and apoptosis (56). Hsp90 inhibitor 17-AAG arrests cell cycles of lung cancer A549 and H446 cells at the G2/M phase and promotes apoptosis via regulating the expression of apoptosis-related proteins (Bax and Bcl-2) (57), and combination of 17-AAG and carbon ions shows treatment efficacy in lung cancer, which results in a definite G2 cell cycle delay (58). Geldanamycin and 17-AAG inhibit the growth of lung cancer cell lines via inducing G2/M arrest concomitant with decreased protein levels of Cdc25C and Cdc2 (51). CDBT exerts an antitumor activity in P-gp overexpressing drug-resistant NSCLC H460TaxR cells by the destabilization of microtubules, degradation of CRAF-1 and ErbB2 and phosphorylated AKT (44), leading to cell cycle arrest at the G2/M phase and reinforcement of apoptosis (59). Hsp90 inhibition of IPI-504 results in disruption of EML4-ALK and inhibition of its downstream signaling pathways, which induces growth arrest and apoptosis in cells carrying the EML4-ALK fusion (60). Hsp90 inhibitor PU-H71 upregulates Grp94, Grp78, ATF4 and CHOP, inducing apoptosis of lung cancer cells by downregulation of Bcl-2, upregulation of Bax, release of cytochrome *c* and activation of caspases (61).

Hsp90 regulates the growth of lung cancer via EGFR-related signaling pathways. As shown in Fig. 4, Hsp90 inhibitor, 2',4'-dimethoxychalcone (1b) suppresses the growth of Iressa-resistant NSCLC H1975 cells by downregulating EGFR, Met, Her2, AKT, and Cdk4, and upregulating Hsp70 (62). Hsp90 inhibitor AUY922 inhibits the proliferation of lung cancer cells and induces cell death by downregulation of EGFR, Met, and AXL, leading to disruption of AKT signal (63). Furthermore, AUY922 results in obvious exhaustion of EGFR, Met, HER2 and AKT in NSCLC cell lines, giving rise to a reinforcement of apoptosis (64). Hsp90 inhibitor WK88-1 reduces the cell survival of lung cancer cells via reducing the expression of EGFR, ErbB2, ErbB3, Met and Akt (65), and combination treatment of Hsp90 inhibitor ganetespib and erlotinib stabilizes the expression state of EGFR inactivation and disrupts ERK and AKT signaling activity (66). Hsp90 inhibitor 17-DMAG inhibits the growth of Ma-1/HGF cells, H1975 cells and PC-9 cells by downregulating EGFR and Met (67) and exhausting EGFR, AKT, MAPK, Cdk4, and cyclin D1 in EGFR-mutant cell lines (68). Hsp90 inhibitors SNX-2112 and SNX-5422 alone and in combination with erlotinib suppresses EGF activation of pAKT(473) and pSTAT3(705), pERK1/2 and pS6 and decreases EGF cross-talk and activation of the c-Met receptor (69). Gamabufotalin inhibits the chaperone function of Hsp90 by reducing expression of Hsp90-dependent client protein EGFR (45). Hsp90 inhibitor HDN-1 binds to C-terminus of Hsp90α and degrades multiple oncoproteins, promoting EGF-induced wild-type and mutated EGFR down-regulation (70).

Hsp90 regulates the growth of lung cancer via RAS-RAF-MEK-ERK-MAPK, PI3K/AKT, TGF and VEGF signaling pathways. As shown in Fig. 5, Hsp90 inhibitor AUY922 inhibits the signals of PI3K-AKT-mTOR and RAF-MEK-ERK and exerts antitumor activity (71). 17-DMAG reduces the survival of SCLC cell lines via downregulating proto-oncogene c-RAF (72) and also reduces XRCC1 expression via inactivation of ERK1/2 and AKT enhancing antitumor activity of gefitinib (73). Defects or polymorphisms of MSH2 correlates with lung cancer, 17-AAG leads to enhanced cytotoxic effect accompanied by the reduction of MSH2 via downregulation of the MKK3/6-p38 MAPK signal and inactivation of p38 MAPK (74). In addition, 17-AAG leads to a decrease of cellular thymidine phosphorylase via ubiquitin-26S proteasome pathway with downregulation of phosphorylated MKK1/2-ERK1/2 and AKT protein levels (75). Hsp90 inhibitor CUDC-305 leads to the degradation of RTKs, and disrupts the signaling molecules of the PI3K/AKT and RAF/MEK/ERK pathways, with concurrent induction of apoptosis (76). Hsp90 inhibitor deguelin reveals an anti-Hsp90 activity and keeps a lid on the expression of a number of client proteins of Hsp90, which is involved in the PI3K/AKT pathway (77). Inhibition of Hsp90 by CS-6 prohibits lung cancer growth by targeting IKKβ/NF-κB, which reduces the expressions of hTERT, HIF-1α, VEGF, CDK4, HER2, p-Akt, cyclin D1, p110α and p-p85 (45). Hsp90 inhibitor L80 disrupts the correlation of HIF-1α and Hsp90 by reducing HIF-1α, VEGF and IGF2 (78). Hsp90 inhibition by CH5164840 with erlotinib treatment abolishes phosphorylation of Stat3 in lung cancer cells, which downregulates ERK signaling (79). Repair protein Rad51 protects NSCLC cells against chemotherapeutic cytotoxicity, but Hsp90 inhibitor 17-AAG cuts down the levels of Rad51 and decreases the phosphorylation of MKK1/2-ERK1/2 (80). Furthermore, Hsp90 inhibition caused by ganetespib shows an obvious cell killing in lung cancer cells, with concomitant destabilization of KRAS signaling effectors, and combination of ganetespib and MEK or PI3K/mTOR inhibitors leads to a remarkable cytotoxic activity (81).

Some new molecular signals involved in network of Hsp90 in lung cancer. As shown in Fig. 6, Hsp90 inhibitor 17-AAG downregulates the expression of MSH2 in human lung cancer and its combination with tamoxifen reinforces cytotoxicity and cell growth inhibition synergistically via reducing MSH2 expression (82). As a potent proteasome inhibitor, PS-341 inhibits various types of cancer, interestingly, Hsp90 inhibitor 17-AAG enhances PS-341-induced lung cancer cell death by degrading upstream regulators of IκB, IRAK-1, and IκB kinases (IKKs) (83). In addition, combination of 17-DMAG and TNF brings about synergistic killing of lung cancer cells via downregulation of IKKβ (84). Hsp90 inhibitor ganetespib induces loss of EML4-ALK expression and depletion of multiple oncogenic signaling proteins in ALK-driven NSCLC cells (85). Inhibition of Hsp90 by NVP-AUY922 suppresses the growth of NSCLC cells, which involves a wide range of cellular functions via consistently decreasing the levels of dihydrofolate reductase (86). Cellular FLICE-inhibitory protein (long form, c-FLIPL) is a critical negative regulator of death receptor-mediated apoptosis, however, depletion of Hsp90α/β decreases c-FLIPL level, and combination of 17-AAG and celecoxib reinforces this results by caspase activation (87). Ganetespib blocks Hsp90 to bind to biotinylated geldanamycin and disintegrates the relation of Hsp90 with its co-chaperone, p23, which inhibits the growth of lung cancer (88). Hsp90 inhibitor deguelin binds to the ATP-binding pocket of Hsp90 and disrupts Hsp90 function by ubiquitin-mediated degradation of HIF-1α (89). Moreover, combination of 17-AAG and TNF induces apoptosis-related cell death of lung cancer cells by degrading RIP and IKKβ that, in turn, blocks TNF-induced NF-κB activation (90).

6. Hsp90-dependent radiosensitization in treatment of lung cancer

The combined treatment of Hsp90 inhibitors and conventional photon radiation has shown more effective tumor growth inhibition than radiation alone, and a number of Hsp90 inhibitors are also known to sensitize cancer cells to radiation. Hsp90 inhibitor ganetespib sensitizes NSCLC cells to radiation (91) via potentiating the effect of radiotherapy and eliminating radioresistant residual cells (49). A purine-scaffold Hsp90 inhibitor, PU-H71, promotes the sensitivity of the lung cancer cells to radiation by inhibiting the repair of DSBs (92). 17-AAG and 17DMAG (Hsp90 inhibitors) have been reported to be potent radio-sensitisers, achieving radiation enhancement ratios ranging from 2.3 to 2.7 (93). Co-treatment of 17-DMAG with radiation has a synergistic antitumor activity in NSCLC cells, which involves in inhibition of DNA repair and correlates with the BER and ATM-regulated pathways (94). Combination of irradiation

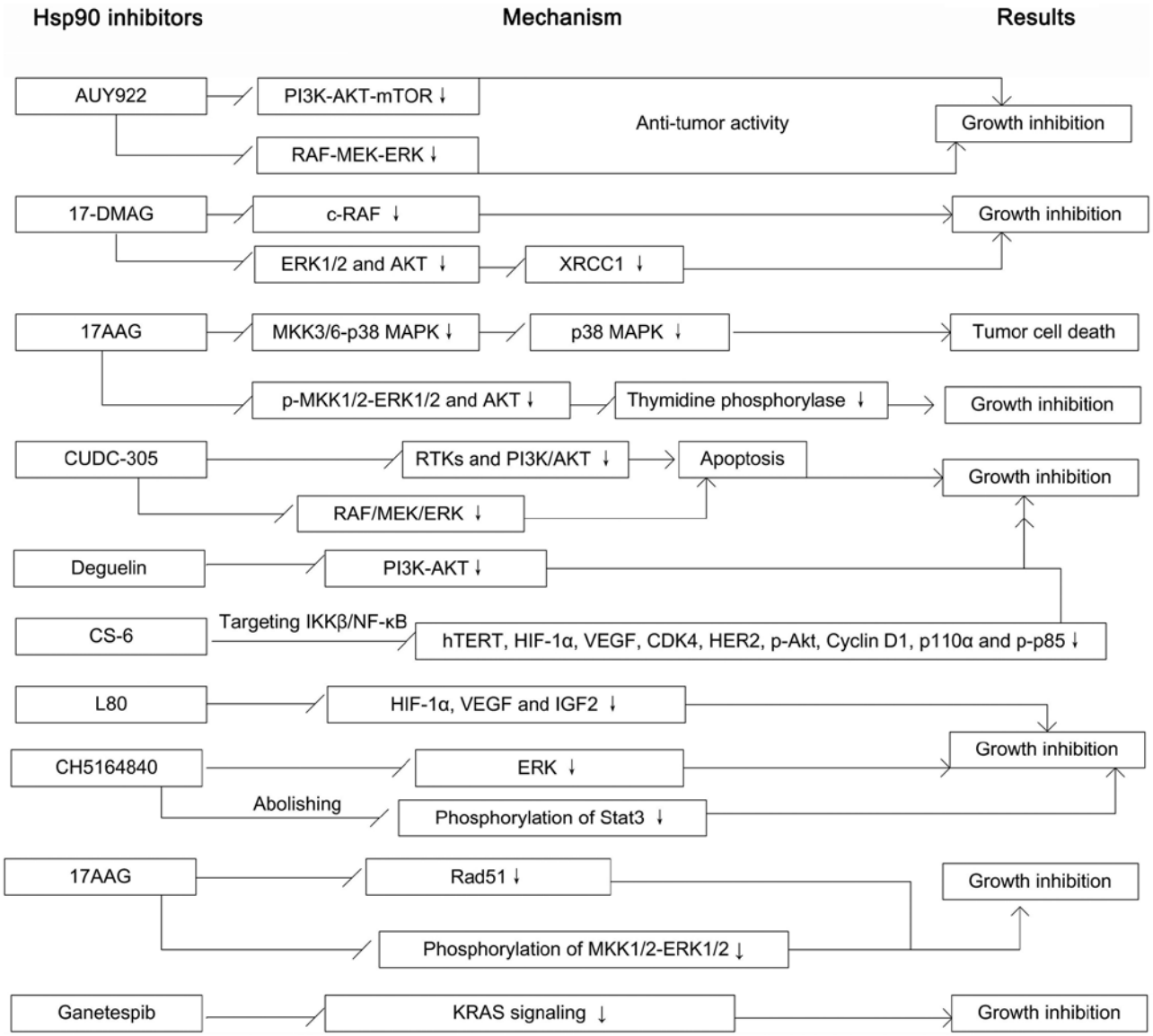

Figure 5. Hsp90 regulates the growth of lung cancer via RAS-RAF-MEK-ERK-MAPK, PI3K/AKT, TGF and VEGF signaling pathways. Hsp90 inhibition inhibits the signals of PI3K-AKT-mTOR and RAF-MEK-ERK and thus impedes the growth and proliferation of NSCLC cells. Inhibition of Hsp90 reduces the survival ability of SCLC cells via downregulating expression of proto-oncogene c-RAF and inactivation of ERK1/2 and AKT as well as the reduction of XRCC1. Hsp90 inhibition leads to cytotoxic effect to NSCLC cells and accompanies with the reduction of MSH2 via downregulation of the MKK3/6-p38 MAPK signal and inactivation of p38 MAPK and leads to downregulation of cellular TP via a ubiquitin-26S proteasome pathway, which is accompanied by a downregulation of phosphorylated MKK1/2-ERK1/2 and AKT protein levels. Hsp90 inhibition give rise to degradation of RTKs, and disrupts the signaling molecules of the PI3K/AKT and RAF/MEK/ERK pathways. Inhibition of Hsp90 targets IKKβ/NF-κB to prohibit lung cancer growth, and reduces the expressions of hTERT, HIF-1α, VEGF, CDK4, HER2, p-Akt, cyclin D1, p110α and p-p85. Disruption of Hsp90 function leads to the disruption of correlation between HIF-1α and Hsp90 by reducing HIF-1α, VEGF and IGF2. Hsp90 inhibition abolishes phosphorylation of Stat3 and give rise to downregulation of ERK signaling. Hsp90 inhibition cuts down the levels of Rad51, phosphorylated MKK1/2-ERK1/2 and damages the correlation of Hsp90 and Rad51 and leads to a remarkable cytotoxic activity via destabilization of KRAS signaling. Hsp90, heat shock protein 90; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; AKT, anaplastic lymphoma kinase; mTOR, mammalian target of rapamycin; RAF, rapidly accelerated fibrosarcoma gene; MEK, mitogen-activated protein kinase; ERK, extracellular-signal-regulated kinase; c-RAF, threonine protein kinase; XRCC1, X-ray repair cross-complement group 1 protein; MKK3, a dual-specificity protein kinase of the STE7 family; MAPK, mitogen-activated protein kinase; TP, thymidine phosphorylase; RTKs, receptor tyrosine kinases; IKKβ, inhibitor of nuclear factor κB kinase; NF-κB, nuclear factor κB; hTERT, human telomerase reverse transcriptase; HIF-1α, hypoxia-inducible factor-1; VEGF, vascular endothelial growth factor; HER2, human epidermal growth factor receptor-2; p110α, enhanced phosphoinositide 3-kinase; IGF2, insulin-like growth factor 2; Rad51, DNA double strand break repair gene.

and 17-AAG displays an additive effect on cell growth inhibition by downregulating the expressions of Cdc25C and Cdc2 (51). Hsp90 inhibitor NVP-AUY922 results in radiosensitization, which is accompanied by DNA repair effect, cell cycle progression and abrogation of homologous recombination (95). Co-treatment of NVP-AUY922 and 17-AAG leads to upregulation of HIF-1α and thus shows a promotion of radiosensitivity (96). Especially, celastrol disrupts the ATP-binding activity of Hsp90, and thus reinforces the radiation-induced cell killing by decreasing levels of EGFR, ErbB2 and survivin and increasing p53 expression (97). Hsp90 inhibitor deguelin suppresses radioresistant lung cancer cells and combined treatment of radiation with deguelin cuts down the viability and vascularization of

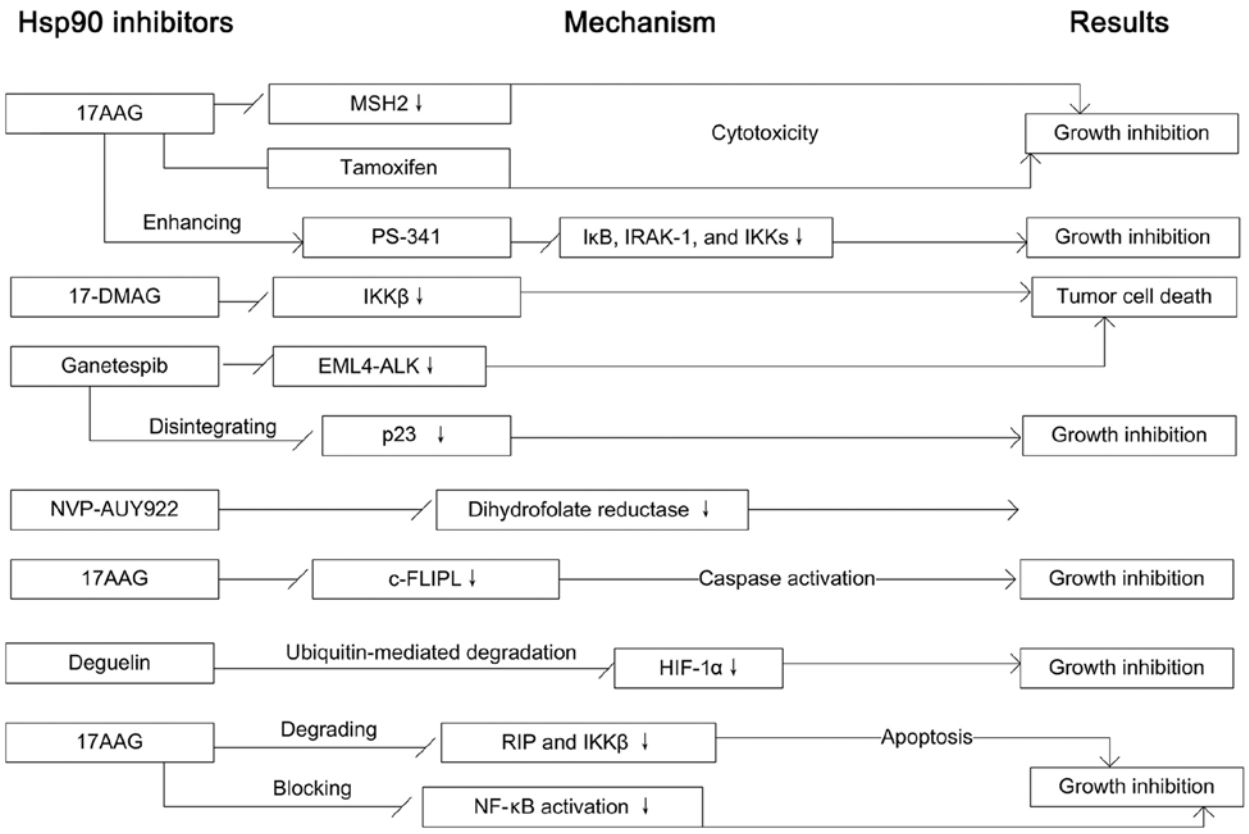

Figure 6. New signaling pathways of inhibition of Hsp90 for regulating the growth of lung cancer. Hsp90 inhibition downregulates the expression of MSH2 and tamoxifen combined with Hsp90 inhibition give rise to cytotoxicity and cell growth inhibition synergistically in NSCLC cells via reducing MSH2 expression. Hsp90 inhibition enhances PS-341-induced lung cancer cell death by degrading IκB, IRAK-1 and IKKs. Combination treatments of Hsp90 inhibition and TNF brings about synergistic killing of lung cancer cells via downregulation of IKKβ. Hsp90 inhibition induces loss of EML4-ALK expression and depletion of multiple oncogenic signaling proteins in ALK-driven NSCLC cells. Hsp90 inhibition disintegrates the relation of Hsp90 with p23 and depletion of Hsp90α/β decreases c-FLIPL level and combination of Hsp90 inhibition and celecoxib reinforces this effect by caspase activation, and leads to ubiquitin-mediated degradation of HIF-1α. Combination of Hsp90 inhibition and TNF induces apoptosis-related cell death of lung cancer cells by degradation of RIP and IKKβ and blocking of TNF-induced NF-κB activation. Hsp90, heat shock protein 90; MSH2, human MutS homolog 2; PS-341, a potent proteasome inhibitor; IκB, IκB kinase; IRAK-1, IL-1R-associated kinase-1; IKKs, IκB kinases; IKKβ, inhibitor κB kinase β; EML4-ALK, echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase; ALK, anaplastic lymphoma kinase; c-FLIPL, cellular FLICE-inhibitory protein; p23, important co-chaperone for the Hsp90; HIF-1α, hypoxia-inducible factor-1; RIP, receptor-interaction proteins.

radioresistant cells by blocking the HIF-1α/Hsp90 interaction and HIF-1α expression (98).

7. Hsp90 and drug resistance of lung cancer

Hsp90 and drug resistance of traditional chemotherapy. As shown in Table II, upregulated Hsp90 has been investigated in connection with the chemoresistance to cisplatin in LAC cells (50), however, inhibition of Hsp90 increases the sensitivity of cells to cisplatin by inducing AMH and AMHR2 expression (99). Hsp90 inhibitor 17-AAG increases the cisplatin-induced cell-killing via suppressing TP expression and activation of ERK1/2 and AKT (75). Hsp90 inhibitor L80 suppresses the proliferation, survival, and migration of lung cancer cells acquired resistance to paclitaxel (78). Hsp90 inhibitor ganetespib facilitates the cell-killing activity of paclitaxel and docetaxel in NSCLC models (100) and 17-AAG reinforces the cytotoxic effect of etoposide by inhibiting the expression of ERCC1 (101). Also, Hsp90 inhibitor STA-8666 combines a chemical moiety targeting active Hsp90 fused via cleavable linker to active metabolite of irinotecan SN38, thus strongly promotes the antitumor activity of carboplatin (56).

Hsp90 and drug resistance of molecular targeted therapy. As shown in Table II, some Hsp90 inhibitors show activity of reversing molecular targeting drug resistance and synergism. FS-108 circumvents gefitinib resistance in EGFR mutant NSCLC cells through inducing G2/M phase arrest and apoptosis (55). AUY922 inhibits growth of EGFR-TKI resistant cell lines by inducing cell programmed death (63) and also displays activity against the gefitinib-resistant sublines with T790M mutation and Met amplification (102). WK88-1 reverses gefitinib resistance by interfering the EGFR or c-Met stability and functions (65). 17-AAG represents a better efficacy for treating NSCLC with acquired resistance to EGFR TKIs (103) and the combination of gefitinib and 17-AAG increases NSCLC cell growth inhibition (73). SH-1242 targets those cells that are chemoresistant or harbor KRAS mutations (104) and exerts cytotoxicity to lung cancer cells. Pyruvate kinase M2 (PKM2) interacts with mutant EGFR and Hsp90 contributing to EGFR-dependent tumorigenesis and facilitates to overcome drug resistance to EGFR TKIs (105). 2',4'-dimethoxychalcone (1b) restrains the proliferation of iressa-resistant NSCLC cells by circumventing the drug-resistance acquired by Met amplification and EGFR mutations (62). Ganetespib shows a

Table II. The research progress of Hsp90 and anti-lung cancer drugs.

Authors/Refs.	Type of lung cancer	Cell lines	Anticancer drugs	Notes
Gomez-Casal *et al* (49)	NSCLC	T2821, T2851	Cisplatin	Hsp90 inhibition can potentiate the effect of radiotherapy and eliminate radioresistant and cisplatin-resistant residual cells
Wang *et al* (55)	NSCLC	HCC827/GR6, NCI-H1650, NCI-H1975	Gefitinib	Targeting Hsp90 with FS-108 circumvents gefitinib resistance in EGFR mutant non-small cell lung cancer cells
Gaponova *et al* (56)	SCLC	NCI-H69, NCI-H157	Carboplatin	STA-8666 strongly enhances the action of carboplatin
Zhang *et al* (59)	NSCLC	H460	Unavailable	CDBT was discovered to have potent antitumor activity in P-gp overexpressing drug-resistant NSCLC H460TaxR cells
Seo (62)	NSCLC	H1975	EGFR TKIs	The 2',4'-dimethoxychalcone (1b) could serve as a potential therapeutic lead to circumvent the drug resistance acquired by EGFR mutation and Met amplification
Choi *et al* (63)	NSCLC	HCC827/GR, HCC827/ER	Gefitinib, erlotinib	AUY922 treatment effectively suppresses proliferation and induces cell death in both resistant cell lines
Smith *et al* (66)	NSCLC	NCI-HCC827, NCI-H1975	Erlotinib, afatinib	Ganetespib potentiates the efficacy of erlotinib in TKI-sensitive, mutant EGFR-driven xenograft tumors and enhances antitumor responses to afatinib
Koizumi *et al* (67)	NSCLC	H1975 cells, PC-9, Ma-1 cells	Erlotinib	Hsp90 inhibition overcomes HGF-triggering resistance to EGFR-TKIs erlotinib in EGFR-mutant lung cancer
Park *et al* (71)	NSCLC	H23, H358, H647, H1944, A549	Trametinib	The Hsp90 inhibitor, NVP-AUY922, sensitizes KRAS-mutant NSCLC with intrinsic resistance to MEK inhibitor, trametinib
Tung *et al* (73)	NSCLC	A549, H1975	Gefitinib	Downregulation of ERK1/2 and AKT-mediated XRCC1 expression by Hsp90 inhibition enhances the gefitinib-induced cytotoxicity in human lung cancer cells
Bao *et al* (76)	NSCLC	H1975, A549	Erlotinib	Hsp90 inhibitor CUDC-305 exhibits durable inhibition of multiple oncoproteins and induction of apoptosis in erlotinib-resistant NSCLC cells
Lee *et al* (78)	NSCLC	H1299, A549, BEAS-2B	Paclitaxel	L80 shows significant inhibitory effects on the viability, colony formation, angiogenesis-stimulating activity, migration, and invasion of a panel of acquired resistance to paclitaxel lung cells
Ono *et al* (79)	NSCLC	NCI-H1975	Erlotinib	CH5164840 enhances the antitumor activity of erlotinib against NCI-H292 EGFR-overexpressing xenograft models
Sang *et al* (85)	NSCLC	H2228, U118-MG	Crizotinib	Targeted inhibition of the molecular chaperone Hsp90 overcomes ALK inhibitor resistance in NSCLC

Table II. Continued.

Authors/Refs.	Type of lung cancer	Cell lines	Anticancer drugs	Notes
Wang *et al* (91)	NSCLC	H460, A549, H1299, H1650, H358, H2087	Carboplatin, paclitaxel	Hsp90 inhibitor ganetespib sensitizes NSCLC to radiation but has variable effects with chemoradiation
Beck *et al* (99)	NSCLC	A549, H1299	Cisplatin	EMT associated with depletion of AMH or AMHR2 results in chemoresistance but sensitizes cells to the Hsp90 inhibitor ganetespib
Hashida *et al* (102)	NSCLC	HCC827, PC-9	Gefitinib	Hsp90 inhibitor NVP-AUY922 enhances the radiation sensitivity of lung cancer cell lines with acquired resistance to EGFR-tyrosine kinase inhibitors
Sawai *et al* (103)	NSCLC	H1650, H1975, H3255	Paclitaxel	Inhibition of Hsp90 downregulates mutant EGFR expression and sensitizes EGFR mutant tumors to paclitaxel
Yang *et al* (105)	NSCLC	A549, H157, H1355, H1975, HCC827	EGFR TKIs	PKM2 depletion suppresses the growth of TKI-resistant xenografts (H1975) that carried L858R/T790M mutations by interacting with Hsp90
Chen *et al* (106)	NSCLC	Unavailable	Crizotinib	Hsp90 inhibition (17-DMAG) can overcome both primary and acquired crizotinib resistance
Tanimoto *et al* (107)	NSCLC	H2228, H3122	Alectinib	Receptor ligand-triggered resistance to alectinib and its circumvention by Hsp90 inhibition in EML4-ALK lung cancer cells
Proia *et al* (100)	NSCLC	H1975	Paclitaxel, docetaxel	Ganetespib potentiates the cytotoxic activity of paclitaxel and docetaxel in NSCLC models. resulting synergistic antiproliferative effects *in vitro* and *in vivo*
Tsai *et al* (101)	NSCLC	H1975, A549	Etoposide	17-AAG could decrease the etoposide-induced p38 MAPK-mediated ERCC1 expression and augment the cytotoxic effect and growth inhibition by etopsoside
Rolfo *et al* (108)	NSCLC	Unavailable	Crizotinib	Hsp90 inhibitors may overcome crizotinib resistance by decreasing proper folding of ALK fusion protein

FS-108, Hsp90 inhibitor; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; AMH, anti-Müllerian hormone; AMHR2, anti-Müllerian hormone II receptor; STA-8666, developed drug; NSCLC, non-small cell lung cancer; KRAS, Kras gene; MEK, mitogen-activated protein kinase kinase; TKIs, tyrosine kinase inhibitors; PKM2, pyruvate kinase M2; L80, Hsp90 inhibitor; Met, Met gene; ALK, anaplastic lymphoma kinase; AUY922, Hsp90 inhibitor; ERK, extracellular-signal-regulated kinase; XRCC1, X-ray repair cross-complement group 1 protein; CDBT, Hsp90 inhibitor; WK88-1, Hsp90 inhibitor; EML4-ALK, echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase; CH5164840, Hsp90 inhibitor; HGF, human growth factor; 17-AAG, Hsp90 inhibitor; MAPK, mitogen-activated protein kinase; ERCC1, excision repair cross-complementing group 1; CUDC-305, Hsp90 inhibitor.

remarkable ability to defeat multiple forms of crizotinib resistance, including secondary ALK mutations (85). 17-DMAG can circumvent both primary and acquired crizotinib resistance (106). Ganetespib promotes the antitumor activity of erlotinib in erlotinib-resistant NCI-H1975 xenografts and also increases efficacy of afatinib (66). CH5164840 can increase the anticancer activity of erlotinib against NCI-H292 EGFR-overexpressing xenograft models (79). CUDC-305 induces apoptosis and inhibits cancer growth of erlotinib-resistant NSCLC cells (76). CDBT has been discovered to have a potent activity against P-gp overexpressing drug-resistant NSCLC H460TaxR cells (59). Hsp90 inhibitors also overcome ligand-triggered resistance to new generation ALK inhibitors and may bring improved benefit for NSCLC patients with EML4-ALK (107,108).

8. Clinical research on Hsp90 inhibitors for treating lung cancer

The potential anticancer activity of some Hsp90 inhibitors for treating lung cancer has been proven in preclinical *in vitro* and *in vivo* models. For instance, recently a clinical trial evaluated the activity and safety of Hsp90 inhibitor ganetespib in combination with docetaxel in advanced NSCLC, which showed that combination of ganetespib significantly prolongs the PFS and OS and the combination treatment of ganetespib and docetaxel does not have obvious additional side effects (109). NSCLC patients in a previous study were divided into three groups: cohort A (EGFR mutants), B (KRAS mutants), or C (with out mutations of both). Patients of the three groups were all administered ganetespib of 200 mg/m^2 via intravenous infusion (1/week; rest for a week after 3 weeks), until disease progression. The results showed that ganetespib monotherapy presents a manageable side effect profile as well as clinical activity in heavily pretreated patients with advanced NSCLCs, particularly in patients with tumors harboring ALK gene rearrangement (110). Another prospective, non-randomized, multicenter, phase II study of IPI-504 monotherapy has shown that IPI-504 has certain clinical activity in patients with NSCLC, particularly among patients with ALK rearrangements (111). However, the clinical research on the Hsp90 inhibitor for treating lung cancer is only at the beginning, it seems that these studies did not produce an impressive breakthrough as we expected. Because Hsp90 conduces to the maturation and stability many mutated or overexpressed oncogenic proteins, targeting Hsp90 has been considered as an effective anticancer therapy. Although the WCLC2016, GALAXY-2 study showed that the addition of ganetespib as a rescue treatment on the basis of docetaxel did not improve efficacy. The combination application of Hsp90 inhibitors and other traditional chemotherapy is still greatly worthy of further exploration. However, the clinical research of Hsp90-dependent molecular targeted therapy (Hsp90 inhibitors) is an area where we have really fallen far behind. We must acknowledge that the main reason of leading to the embarrassing situation correlates with medical ethics and strict approval system of new drugs in all countries; after all, we are faced with humans. However, clinical research and application is the only way and the ultimate goal. Only this way, can we bring benefits to lung cancer patients from Hsp90 inhibitors.

9. Perspective and limitation

The clinical benefit of current anticancer regimens for lung cancer therapy is still limited due to moderate efficacy, drug resistance, and early recurrence. Therefore, the development of effective new anticancer drugs for first-line therapy and for optimal second-line treatment is necessary. Study on the molecular mechanism of Hsp90 in lung cancer has made some progress as well as greatly promoting the development of Hsp90-dependent molecular targeted drugs. However, there are some shortcomings in current research. So far, no large sample numbers and multiple centers on the expression of Hsp90 in lung cancer are reported, including in lung tissues, blood, bronchoalveolar lavage fluid and malignant pleural effussion. In addition, no studies keep a watchful eye on gene mutations and copy abnormality of Hsp90, which may be correlated with the efficacy of Hsp90 inhibitors such as EGFR mutations. Importantly, although clinical studies to evaluate the activity and safety of Hsp90 inhibitors in treating lung cancer patients has been reported occasionally, it seems that quality and scale of these studies could not support the evidence of clinical application of Hsp90 inhibitors. To assess whether Hsp90 inhibitor proves to be a successful therapeutic strategy in treating lung cancer patients, we still need to do further research, such as construction of drug delivery vehicles, design of clinical research and evaluation of side effects. Future research should focus on assessing the activity and safety of Hsp90 inhibitors in clinical lung cancer patients and establish the most effective Hsp90 inhibitors for treating lung cancer.

10. Conclusion

Research shows that Hsp90 is highly expressed in lung cancer and that upregulation of Hsp90 potentially facilitates proliferation and metastasis of lung cancer. However, anti-Hsp90 (Hsp90 inhibitors) studies have demonstrated that downregulation and function disruption of Hsp90 inhibits cell proliferation, motility and metastasis, and induces apoptosis of lung cancer cells. However, there is an urgent need for a comprehensive assessment of Hsp90 protein expression and gene abnormality in large cohorts of lung cancer. In addition, high quality clinical research on Hsp90 inhibitors are also needed for evaluating the efficacy and safety in clinical recommendation. Actually, we still know relatively little as to how the Hsp90 regulates tumorigenesis of lung cancer at the molecular level, thus improved understanding of the molecular mechanisms and signaling pathways correlated with Hsp90 present an interesting challenge, and a future important direction.

Acknowledgements

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Abbreviations

17-AAG, Hsp90 inhibitor; 17-DMAG, 17-demethoxygeldanamycin; Hsp90 inhibitor; Abl, Src family tyrosine kinase; Aha1,

activator of Hsp90 ATPase; AKT, anaplastic lymphoma kinase; ALK3, AMHR2 heterodimerizes with type I receptors; AMH, anti-Müllerian hormone; AMHR2, anti-Müllerian hormone type II receptor; APC/C, anaphase promoting complex; ATF4, anti-activating transcription factor 4; AT13387, Hsp90 inhibitor; ATM, ataxia-telangiectasia mutant; ATP, adenosine-triphosphate; ATPase, adenosinetriphosphatease; AUY922, Hsp90 inhibitor; AXL, receptor tyrosine kinase; BAD, Bcl-2-associated death promoter; BALF, bronchoalveolar lavage fluid; Bcl-2, B-cell lymphoma-2; Bax, bcl-2-like protein 4; BER, base excision repair; BMP, bone morphogenetic protein; Cdc2, cell division cycle 2; CDBT, Hsp90 inhibitor; Cdc25C, cell division cycle 25C; Cdc37, cell division cycle 37; Cdk, cyclin-dependent kinase; c-FLIPL, cellular FLICE-inhibitory protein; CHOP, nuclear transcription factor; CH5164840, Hsp90 inhibitor; CK2, casein kinase 2; COX-2, cyclooxygenase-2; CRAF-1, threonine protein kinase; CS-6, Hsp90 inhibitor; Cyp40, cyclophilin 40; CUDC-305, Hsp90 inhibitor; DSBs, DNA double-strand breaks; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EML4-ALK, echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; ErbB2/HER2, human epidermal growth factor receptor-2; ERBB2 YVMA, a 12-bp duplication/insertion of the amino acid sequence YVMA in exon 20 at codon 776; ERCC 1, excision repair cross-complementary 1; ERK, extracellular-signal-regulated kinase; FAK, focal adhesion kinase; Fes, Src family tyrosine kinase; Fkbp51, Hsp90-associated human peptidyl prolyl *cis*/*trans* isomerases; Fkbp52, Hsp90-associated human peptidyl prolyl *cis*/*trans* isomerases; Fps, Src family tyrosine kinase; FS-108, Hsp90 inhibitor; Gp96, a receptor for heat shock protein 90; Grp94, glucose-regulated protein 94; Grp78, glucose-regulated protein 78; HDAC6, histone deacetylase 6; HDACi, histone deacetylase inhibitor; HDN-1, Hsp90 inhibitor; HEY-1, hairy/enhancer-of-split related with YRPW motif protein 1; Her2, human epidermal growth factor receptor-2; HES-1, Hes family BHLH transcription factor 1; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor-1; Hop/Sti1, hop-like stress-induced protein 1 co-chaperone; Hsp90, heat shock protein 90; hTERT, human telomerase reverse transcriptase; IGF-I, insulin-like growth factor 1; IGF2, insulin-like growth factor 2; IκB, IκB kinases; IKKβ, inhibitor of nuclear factor κB kinase; IKKs, inhibit κB kinase complex; IPAK-1, Toll-like receptor-associated kinases; IPI-504, Hsp90 inhibitor; IL-1R, interleukin-1 receptor; IRAK-1, IL-1R-associated kinase-1; kDa, atomic mass unit; Lck, Src family tyrosine kinase; LAC, lung adenocarcinoma; L80, Hsp90 inhibitor; L858R, leucine substitution at amino acid 858; LPLTPLP, Hsp90 inhibitor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; Met, Met gene; MKK, a dual-specificity protein kinase of the STE7 family; MMP, matrix metalloproteinase; MPE, malignant pleural effussion; MSH2, human MutS homolog 2; NF-κB, nuclear factor κB; NVP-AUY922, Hsp90 inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; p110α, enhanced phosphoinositide 3-kinase; p23/Sba1, the protein encoded by the PTGES3 gene; p53, tumor suppressor; p65, transcription factor; P-gp, P-glycoprotein; PKM2, pyruvate kinase M2; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Pih1/Nop17, nucleolus homologous protein 17; PP5, protein phosphatase 5; p-p85, phosphorylated p85; PS-341, proteasome inhibitor; pS6, phosphorylated ribosome protein S6; pSTAT3, phosphorylated signal transducer and activator of transcription 3; PTACH, HDAC inhibitor; PU-H71, Hsp90 inhibitor; Rad51, DNA double strand break repair gene; Raf, rapidly accelerated fibrosarcoma gene; RAS, Ras gene; RTKs, receptor tyrosine kinases; RIP, receptor-interaction proteins; SCC, squamous cell carcinoma; SH-1242, analogue of deguelin; SN38, an antineoplastic drug and is the active metabolite of irinotecan; SNX-5422, Hsp90 inhibitor; Src, Src family kinase; STA-8666, Hsp90 inhibitor; STA-1474, Hsp90 inhibitor; T790M, the 790th site of EGFR exon 20; Tah1, TPR7-containing protein associated with Hsp90; TGF, transforming growth factor; TNF, tumor necrosis factor; TP, thymidine phosphorylase; TRAP1, TNF receptor associated protein 1; Unc45b, unc45 myosin chaperone b; VEGF, vascular endothelial growth factor; WK88-1, Hsp90 inhibitor; XRCC1, X-ray repair cross-complement group 1 protein; Yes, Src family tyrosine kinase.

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