IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2021 Vol.:21, Issue:3

A Review on Current Knowledge: Role of HSP90 in Cancer Biology

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 20 May 2021
Accepted: 26 May 2021
Published: 30 June 2021

www.ijppr.humanjournals.com

Keywords: Chaperone, Heat shock protein 90, Signaling proteins, Targeting HSP90

ABSTRACT

Hsp90 is a molecular chaperone that plays an essential role in many cellular processes including cell cycle control, cell survival, hormone, and other signaling pathways. It is important for the cell's response to stress and is a key player in maintaining cellular homeostasis. In the last ten years, it has become a major therapeutic target for cancer, and there has also been increasing interest in it as a therapeutic target in neurodegenerative disorders, and the development of anti-virals and anti-protozoan infections. The stability and function of many oncogenic mutant proteins depend on heat shock protein90 (HSP90). Oncogene stability and homeostasis mediated by the HSP90 chaperone is a crucial protection trait of cancer cells. Therefore, HSP90 represents an attractive therapeutic target for many cancers, including colorectal cancer. Targeting HSP90 with chemical inhibitors would degrade these oncogenic proteins, and thus serve as useful anticancer agents. This review provides an overview of the HSP chaperone machinery and the structure and function of HSP90. We also highlight the key oncogenic proteins that are regulated by HSP90 and describe how inhibition of HSP90 could alter the activity of multiple signaling proteins, receptors, and transcriptional factors implicated in carcinogenesis.

INTRODUCTION

1.1. Hsp90 (heat shock protein 90) is a chaperone protein that assists other proteins to fold properly, stabilizes proteins against heat stress, and aids in protein degradation. It also stabilizes several proteins required for tumor growth, which is why Hsp90 inhibitors are investigated as anti-cancer drugs. Heat shock proteins, as a class, are among the most highly expressed cellular proteins across all species.[1- 3] as their name implies, heat shock proteins protect cells when stressed by elevated temperatures. They account for 1–2% of total protein in unstressed cells. However, when cells are heated, the fraction of heat shock proteins increases to 4–6% of cellular proteins.[4]Heat shock protein 90 (Hsp90) is one of the most common heat-related proteins. The "90" comes from the fact that it weighs roughly 90 kilo Daltons. A 90 kDa protein is considered fairly large for a non-fibrous protein. Hsp90 is found in bacteria and all branches of eukarya, but it is absent in archaea.[5] Whereas cytoplasmic Hsp90 is essential for viability under all conditions in eukaryotes, the bacterial homolog htpg is dispensable under non-heat stress conditions.[6] This protein was first isolated by extracting proteins from cells stressed by heating, dehydrating, or by other means, all of which caused the cell's proteins to begin to denature. However, it was later discovered that Hsp90 also has essential functions in unstressed cells.[7]

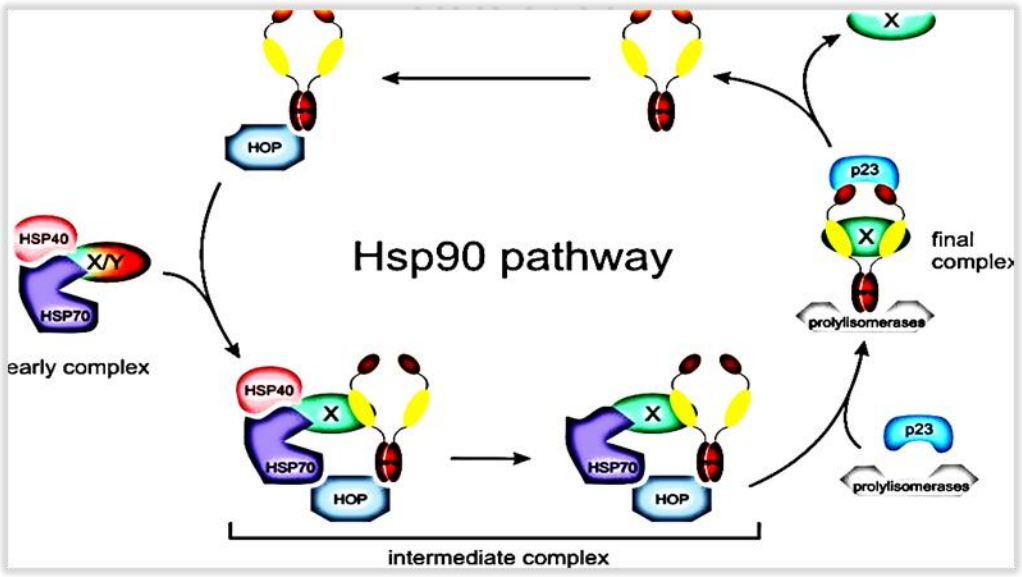

Figure No. 1 Hsp90 Pathway[7]

1.2. Hsp90: Structure and Function.[8]

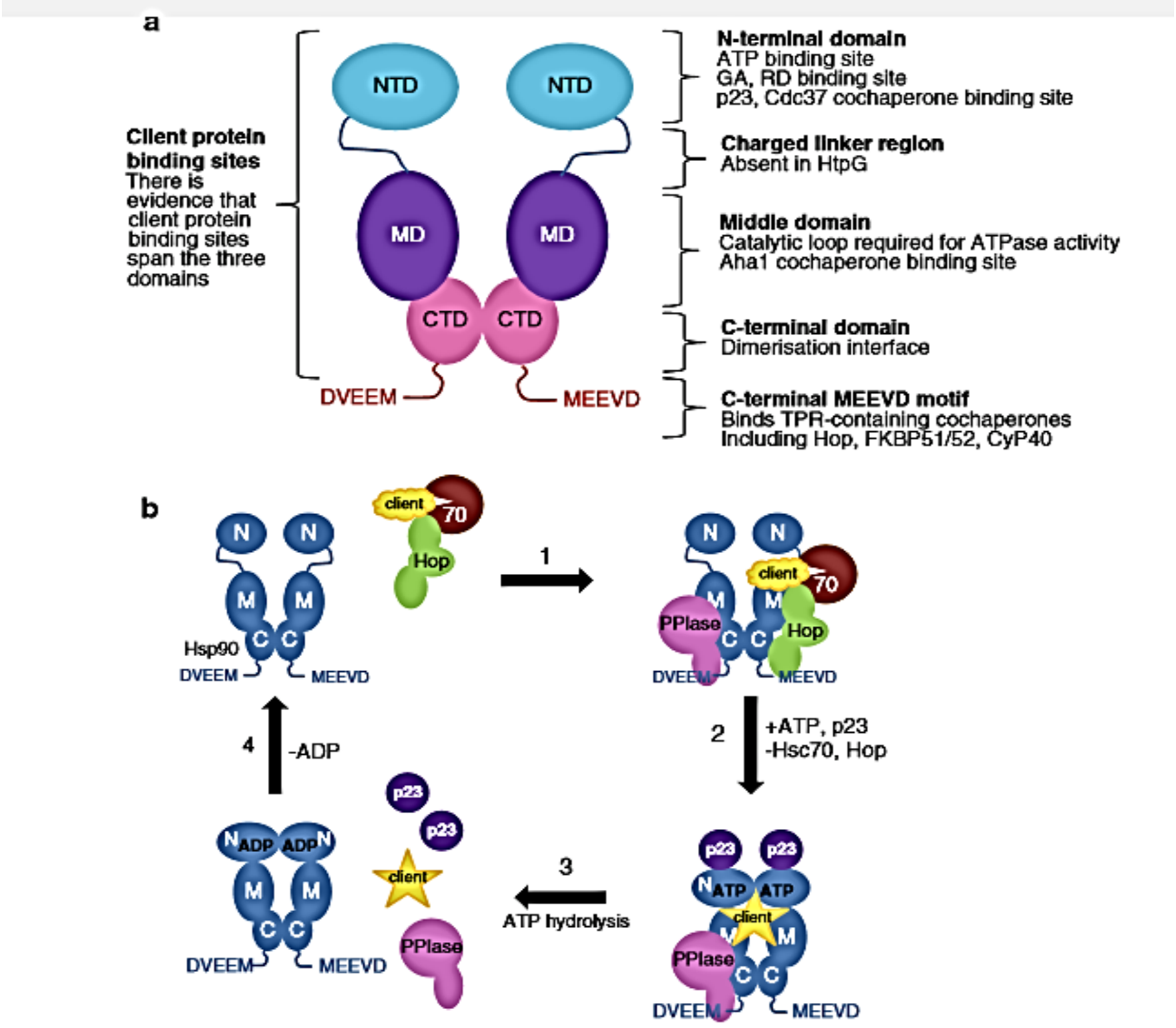

Figure No. 2: Structure and mechanism of Hsp90. (a) Structural domains in the Hsp90 dimer. NTD is the N-terminal domain that binds ATP, GA, RD, and other small molecule inhibitors and which also binds co-chaperones and potentially client proteins. This is followed by an unstructured highly charged linker region which is absent in HtpG. MD is the middle domain that contains a catalytic arginine required for the ATPase activity, binds to co-chaperones, and is thought to be the major client-protein binding site. CTD is the C-terminal domain that contains the major dimerization interface which makes Hsp90 a constitutive dimer. At the C-terminus is a highly conserved MEEVD motif that binds to TPR-containing co-chaperones. (b) The model was proposed for the activation of steroid receptor client proteins (yellow) by the Hsp90 machinery. Hsp90 is shown in blue, Hsp70 in dark red, co-

chaperones include Hop (green), high molecular weight PPIases such as FKBP51, FKBP52, or CyP40 (pink), and the small acidic protein p23 (purple)

1.3. Protein Types of HSP90

The HSP90 family represents a group of well-conserved proteins with an average molecular mass of 90 kDa. There are two major cytosolic Hsp90 isoforms, the inducible Hsp90α1 (HspC1) and the constitutive Hsp90β (HspC3), commonly termed Hsp90.[9, 10] Hsp90 is the major soluble protein of the cell and most commonly located in the cytoplasm. Like many other chaperones, Hsp90 is a rather hydrophobic protein whose hydrophobicity further increases after heat shock.[11,12] The HSP90 family members are encoded by a multigene family encompassing six genes and 11 pseudogenes in humans.[10] Functional genes encoding HSP90 proteins map to human chromosomes 6, 11, 12, 14, and 16.[10]

The most studied genes are *HSP90AA1 (HSPC1)* and *HSP90AB1 (HSPC3)* encoding proteins that differ by eight amino acids. While Hsp90α1 (HspC1) represents the stress-inducible isoform, Hsp90β (HspC3) is a constitutively expressed protein. The genes are clustered on chromosomes 14q32.32 and 6p12, respectively. Two transcript variants encoding different isoforms have been found for the *HSP90A* gene. Grp94 (Hsp90B1, HspC4) is the longest member of the HSP90 family with 803 amino acids characterized by three unique deletions and three unique insertions showing approximately 42% identity and 60% similarity with Hsp90α1 and Hsp90β, respectively.[10] It harbors the highly conserved C-terminal sequence K-D-E-L facilitating its retention in the ER.[13]

1.4. HSP90: Family member

Table No. 1: HSP90s of various pro- and eukaryotic organisms

Gene	Protein	Aliases	UniPort ID	Gene ID
Human				
HSP90AA1 (HSPC1)	HspC1	Hsp90α1, Hsp90AA1, Hsp86, HspCA, Hsp89, Hsp90A, renal carcinoma antigen NY-REN-38	P07900	3320
HSP90AA2 (HSPC2)	HspC2	Hsp90α2, Hsp90AA2, Hsp90α-like 3, HspCA	Q14568	3324
HSP90AB1 (HSPC3)	HspC3	Hsp90β, Hsp90AB1, Hsp84, HSP90B, HspCB	P08238	3326
HSP90B1 (HSPC4)	HspC4	Endoplasmin, Grp94, Gp96, Tra-1, Hsp90B1	P14625	7184
TRAP1 (HSPC5)	HspC5	Trap-1, Hsp75, Hsp90L	Q12931	10131

The human *HSP90* gene family encodes at least five members(Table 2),with the exception of *HSP90N* originally termed Hsp89-α-δ-N.[14]

1.5. Hsp90 & development of cancer[15]

Many oncogenic proteins are HSP90 client proteins. Table 2 depicts the list of client proteins discussed below, the mechanism of actions of these proteins, and potential tumors that HSP90 inhibitors could be applied to

Table No. 2: A selected list of HSP90 client proteins, mechanism of actions of these proteins, and potential target tumors that HSP90 inhibitors could be applied to[15]

Class of protein	Client protein or interacting protein of HSP90	Mechanism of action	Potential target cancer
Receptor tyrosine kinase	EGFR mutant	Activation of downstream prosurvival pathways, such as PI3K-AKT and MAPK	NSCLC and glioblastoma
	ErbB2/HER-2		Breast cancer
	KIT		GIST
Signalling molecules or kinases	AKT	Activation of prosurvival proteins and suppression of proapoptotic proteins	Various cancers
	B-Raf mutant	Constitutively activates ERK signalling	Melanoma
	MET	Involved in cellular proliferation, migration, invasion and morphogenesis	Gastric, lung
	CDK4	Phosphorylates and inactivates Rb, allowing cell cycle to proceed	Tumours with CDK4 overexpression
	Death domain kinase RIP	Allows activation of NF-κB and its antiapoptotic signals	
Transcriptional factors	HIF-1α	Promoting angiogenesis	Renal cancer
	ERα-receptors	Regulating genes involved in cellular proliferation	Breast cancer
	P53 mutant	Transcription of genes involved in cell cycle arrest or apoptosis	Mutated in ~50% of cancer
Chimeric fusion-proteins	BCR-ABL	Activates numerous signal transduction pathways in leukaemogenesis	CML
	NPM-ALK	Induces cell transformation and proliferation	Anaplastic lymphoma
Others	Telomerase	Prevents telomere shortening	Various cancers
	Apaf-1	Crucial for apoptosome formation	
	Bcl-2	Regulates mitochondrial apoptotic pathway	Follicular lymphoma/small cell lung cancer
	MMP2	Facilitates invasion through cell adhesion, matrix digestion and cell migration	Overexpressed in various cancers

CDK4= cyclin-dependent kinase 4; CML¼chronic myeloid leukemia; EGFR¼epidermal growth factor receptor; ER¼oestrogen receptor; GIST¼gastrointestinal stromal tumours; HIF¼hypoxia-inducible factor; HSP¼heat-shock protein; MAPK= mitogen activated protein kinase; NSCLC= non-small cell lung cancer; Rb¼retinoblastoma; RIP¼receptor-interactingprot

1.6. Targeting Hsp90 in cancers[15]

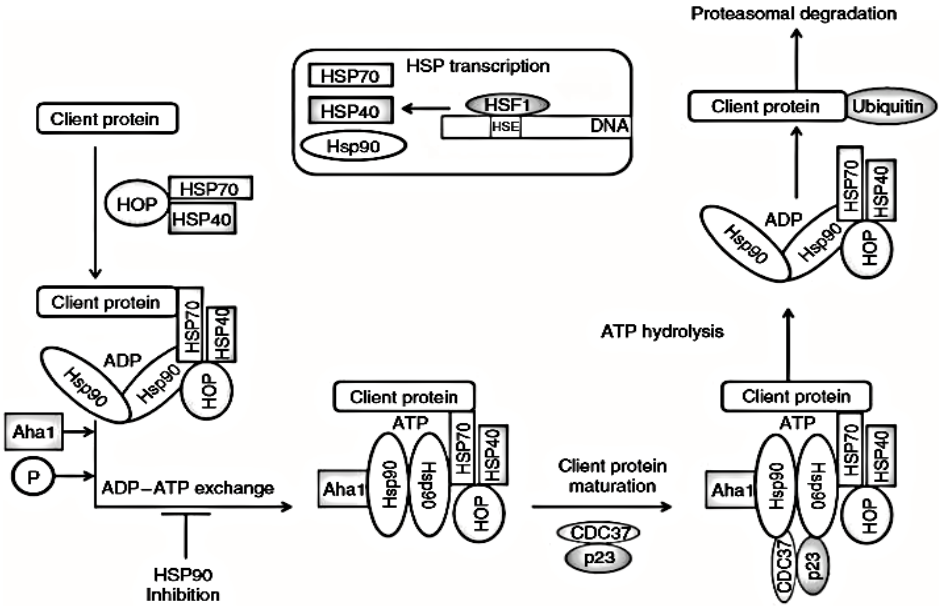

Figure No. 3: The binding of a client protein to HSP90 requires the cooperation of HSP90 with another chaperone, HSP70, and its co-factor HSP40. Both HSP90 and HSP70 chaperones are further linked by an adapter protein called HOP, which binds to both HSP90 and HSP70 through the small helical TPR domains to the C-terminal ends of HSP90 and HSP70. Aha1 is a co-factor that can bind and stimulate the activity of HSP90 ATPase. When HSP90 exchanges ADP for ATP, it undergoes a conformational change, which dissociates from the HSP70/HSP40/HOP complex, allowing ATP-dependent interaction with other cochaperones, such as CDC37 and p23, to form a mature complex. It is in this mature state that HSP90 allows client protein activation following cellular stresses, including phosphorylation of AKT, binding of EGFR to its ligands, and ensuring transcription factors, such as HIF-1a and p53, to express genes. Inhibition of ATP-binding through HSP inhibitors prevents client protein maturation and result in degradation of these oncogenic proteins by the proteasome.

1.7. Cell cycle regulatory proteins[15]

Cellular division is carefully monitored by cell cycle checkpoints, which are regulated by cyclins, cyclin-dependent kinases (CDK), and CDK inhibitors. In addition, retinoblastoma (Rb) and the E2F transcription factor regulate the G1/S transition. Retinoblastoma phosphorylation is crucial to cell cycle progression. When unphosphorylated, Rb blocks cell proliferation by altering E2F function. When phosphorylated, Rb is inactive and so the cell

cycle proceeds.CDK4 phosphorylates Rb and is a client protein of HSP90. Heat-shock protein 90 inhibition targets CDK4 for proteasomal degradation allowing Rb to remain unphosphorylated.

1.8.Hsp90 activation and cell cycle regulation.[16]

Protein	Role in cell cycle	Arrest point	Comments
Cdk1	Triggering mitosis	G_2 checkpoint	Nuclear import also Hsp90-dependent
Cdk2	S-phase entry	G_1/S boundary	MAPK-independent
Cdk4	pRb phosphorylation	G_1 checkpoint	G_1 arrest is Rb-dependent
Cdk6	pRb phosphorylation	G_1 checkpoint	G_1 arrest is Rb-dependent
Cyclin B	Triggering mitosis	G_2 checkpoint	Regulated by clients. Observed in yeast
Cyclin D	pRb phosphorylation	G_1 checkpoint	Not a client but regulated by clients
Cyclin E	S-phase entry	G_1/S boundary	Not a client but regulated by clients
Myt-1	Maintaining G_2	Mitotic catastrophe	Degradation allows entry into mitosis in the presence of DNA damage
Wee-1	Maintaining G_2	Mitotic catastrophe	
Plk1	Centrosome function	Spindle checkpoint	Plk1-Hsp90 not associated in all cells
Aurora B	Regulating mitosis	Polyploidy	Also affects meiosis
Survivin	Regulating mitosis	G_2/M	Possible effects on apoptosis

1.9. Role of HSP90 in Accumulation of Point Mutations[17]

The magnitude of genomic stability in cancer cells can range from single base-pair substitutions to whole chromosome losses or duplications and can arise from both exogenous and endogenous mechanisms Common exogenous causes of genomic instability include exposure to mutagens such as tobacco smoke or ultraviolet radiation Endogenous mechanisms that increase mutational burden include microsatellite instability as a result of loss-of-function mutations in DNA mismatch repair(MMR) proteins, up-regulation of the C-to-U deamination–editing enzyme APOBEC3B, and missense mutations in the exonuclease domains of DNA polymerase POLE and POLD). Cancers harboring these altered DNA repair processes accumulate high levels of somatic mutation, which provides a deep reservoir of genotypes from which tumor-promoting phenotypes can be selected. Evidence from model organisms suggests that the protein folding–based buffer function of HSP90 may influence the accumulation of this genetic diversity by enabling cancer cells to tolerate protein-folding stress associated with the hypermutation. Although not reported to date, experimental testing of this hypothesis in cell culture and animal models would provide useful insights into the role of HSP90 buffering in supporting oncogenesis.

1.9.1. HSP90 as an Anticancer Vaccine[17]

Rather than investigating how HSP90 buffering may allow tumors to adapt and evade immune attack, studies going back as far as the 1980 shave focused primarily on the immunogenic properties and therapeutic potential of purified or enriched preparations of chaperone-bound peptides when presented to the immune system as vaccines. One of the earliest links connecting HSP90 to anti-tumor immune responses was the observation that cytosolic HSP90 and its Endoplasmic reticulum paralog, glucose-regulated protein 94 (GRP94), were presented on the surface of murine tumors as antigens. This surface expression serves as a damage-associated molecular pattern, and its presence on tumor cells is consistent with the model that stressed cells signal to the extracellular environment when they are internally damaged. Purification of HSP90 or GRP94 from tumor cell lysates and subsequent immunization with the purified material has been shown to generate tumor-specific immune responses. Similar observations have also been made with HSP70, supporting the idea that protein folding chaperones bind tumor-specific antigens and might be useful as anticancer vaccines. Importantly, while HSP90 and GRP94 perform important functions in intracellular processes driving antigen presentation, HSP-based vaccines involve the extracellular interaction of HSP-peptide complexes with professional antigen-presenting cells. These cells internalize and process the associated peptides for presentation through MHC class II (to prime CD4+ T cells) or cross-presentation onto MHC class I (to prime CD8+ T cells) While the clinical promise of chaperone vaccines has yet to be realized, their investigation has helped define the role of the protein folding machinery in antigen presentation.

1.9.2. Chaperoning oncogenic pathways in CRC

HSP90 clients regulate cancer-critical mechanisms such as angiogenesis, metastasis, apoptosis, and drug resistance.[18] Indeed, several oncogenic pathways, including transforming growth factor β (TGF-β), mitogen-activated protein kinases (MAPKs), AKT/PI3K, and WNT, are influenced by HSP90 mediated stabilization.[19] **Fig. 4** Of particular clinical relevance to CRC, receptor tyrosine kinases (RTKs) and several of their signaling transducers depend on HSP90 chaperonage. Blockade of the epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and its corresponding RTK receptor VEGFR, have clinical benefit and are part of standard treatment for patients with metastatic CRC.[20, 21] As will be discussed later, preclinical and clinical studies have shown that HSP90 inhibitors

are promising combination partners to RTK blockade, suggesting a clinical relevance for HSP90 inhibition in CRC.[18]

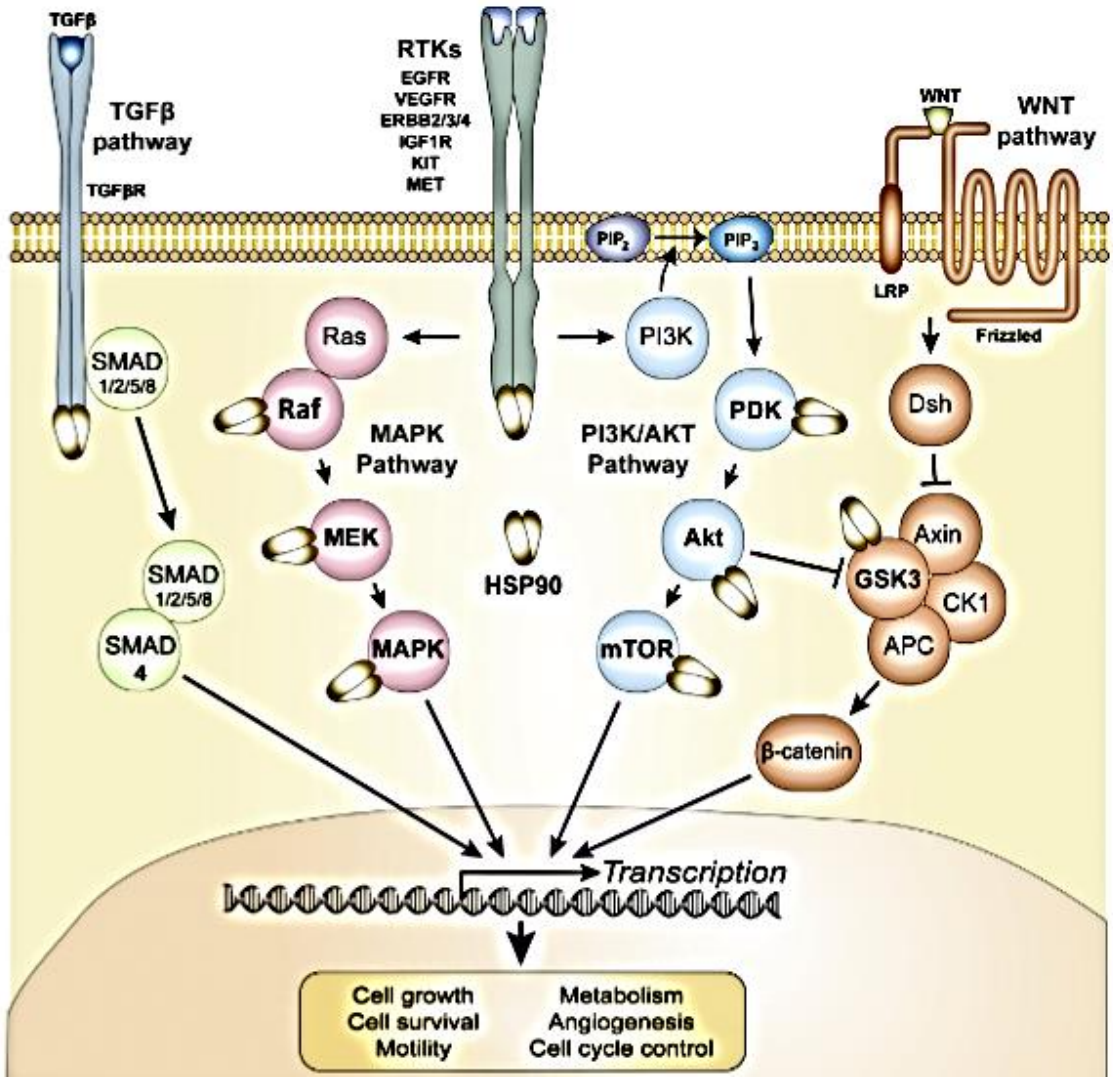

Figure No. 4: HSP90 chaperonage of oncogenic pathways in CRC. Four major oncogenic pathways that drive growth, proliferation, and invasiveness of CRC are simplified and depicted in distinct colors. Receptor and downstream proteins marked in bold followed by an HSP90 molecule indicate signaling mediators that are known HSP90 clients in CRC. HSP90 – Heat shock protein 90; TGF-β – Transforming growth factor-beta; TGFβR – TGF-β receptor; SMAD – Mothers against decapentaplegic homolog; EGFR – epidermal growth factor receptor; VEGFR – vascular endothelial growth factor receptor; ERBB – erythroblast oncogene B; IGF1R – Insulin-like growth factor 1 receptor; KIT – KIT Proto-oncogene receptor tyrosine kinase; MET –MET proto-oncogene receptor tyrosine kinase; Ras – Kirsten rat sarcoma viral proto-oncogene; Raf – Raf proto-oncogene serine/ threonine-protein kinase; MEK – Mitogen-activated protein kinase kinase 1; MAPK – Mitogen-activated protein

kinase; PI3K – Phosphoinositide 3-kinase; PIP2 – Phosphatidylinositol 4,5-bisphosphate; PIP3 – Phosphatidylinositol (3,4,5)-trisphosphate; PDK – Pyruvate dehydrogenase kinase; Akt – Protein kinase B; mTOR – Mechanistic target of rapamycin; Wnt – Proto-oncogene Wnt; LRP – Lipoprotein receptor-related protein; Dsh – Dishevelled protein; GSK-3 – Glycogen synthase kinase 3; CK1 – Casein kinase 1; APC – Adenomatosis polyposis coli.

1.9.3. HSP90 inhibitors in combination with targeted therapy

Among the few targeted therapies used in standard-of-care for metastatic CRC are the monoclonal anti-EGFR antibodies cetuximab and panitumumab, as well as bevacizumab, regorafenib, and Ziv-aflibercept that block angiogenesis mediated by VEGF/VEGFR signaling in the endothelium [22] **Fig. 5.**

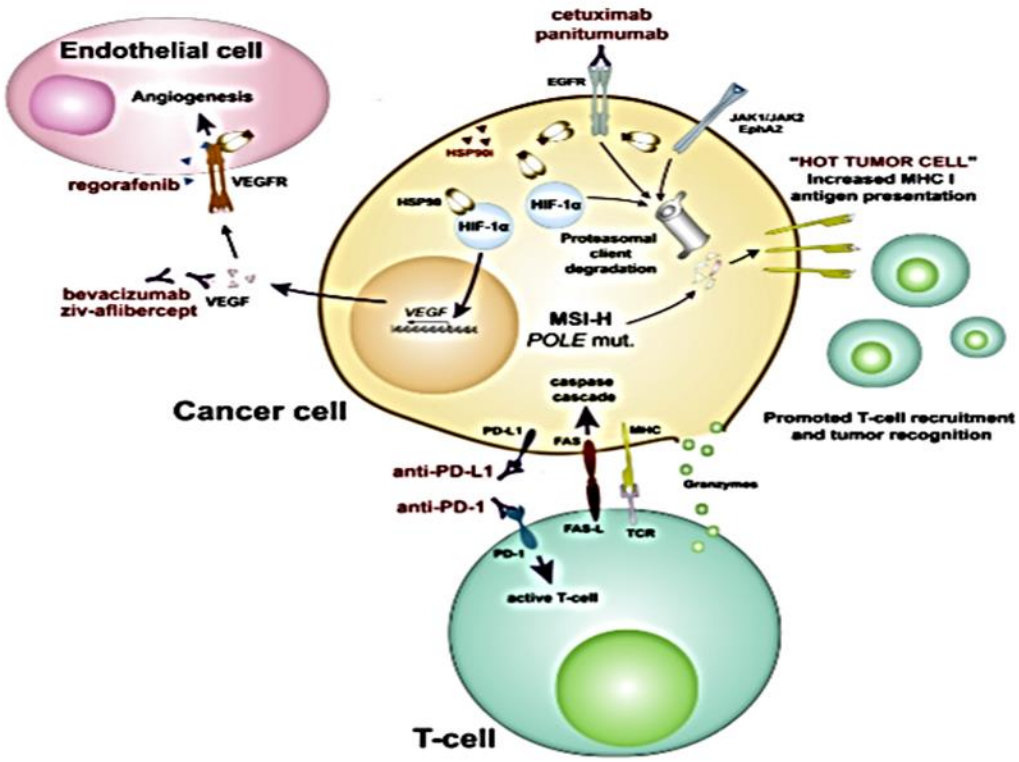

Figure No. 5: HSP90 inhibition can improve targeted therapy and immunotherapy in CRC. Targeted treatment of EGFR-driven CRC is managed by applying anti-EGFR antibodies cetuximab and panitumumab which induce receptor internalization and degradation. Neo angiogenesis VEGF/VEGFR pathway in CRC tumors is blocked using anti-VEGF antibodies bevacizumab or Ziv-aflibercept that sequester VEGF, prohibiting it from binding to the receptor as well as inhibiting VEGF/VEGFR signaling with the tyrosine kinase inhibitor regorafenib. Checkpoint inhibitor antibodies anti-PD1 and anti-PD-L1 allow activation of T-

cell-mediated anti-cancer effects via FAS receptor-mediated apoptosis and granzyme-mediated cancer cell lysis. Increased MHC I mediated antigen presentation improves T-cell recruitment that is fostered by intracellular protein degradation and high-mutational load from MSI phenotype or mutated POLE, thus turning cancer cells immunogenic or "hot". HSP90 inhibitors depicted as red triangles hinder the stabilization process of various HSP90 clients which in turn end in the MHC-I neo-antigen presentation pathway. HSP90 – Heat shock protein 90; EGFR – Epidermal growth factor receptor; HIF-1α– Hypoxia-inducible factor 1-alpha; VEGF – Vascular endothelial growth factor; VEGFR – Vascular endothelial growth factor receptor; MSI-H – Microsatellite instability-high; POLE – Polymerase epsilon; PD-1 – Programmed cell death protein 1, PD-L1 – Programmed death-ligand 1; MHC-I – Major histocompatibility complex class 1; TCR – T-cell receptor; FAS – First apoptosis signal receptor; FAS-L – FAS ligand; JAK1/2 – Janus kinase 1/2; EphA2 – Ephrin type-A receptor 2

1.9.4. Patient stratification to improve the effect of HSP90 inhibition in combination therapies

Although combination therapies including HSP90 inhibitors represent an attractive therapeutic strategy, clinical efficacy is likely to be improved with accompanying biomarkers to identify tumors that are sensitive to chaperone-targeted therapy.[23]**Fig. 6** Considering the limited clinical testing of HSP90 inhibition in CRC, comprehensive analyses of potential predictive factors are pending. However, pre-clinical studies may provide important clues, as has been discussed above for prominent oncogenes such as KRAS and BRAF. Moving towards the multi-molecular approach in precision medicine, consensus molecular subtypes (CMS) provides a new biological framework that classifies CRCs independently of cancer stage.[24,25]

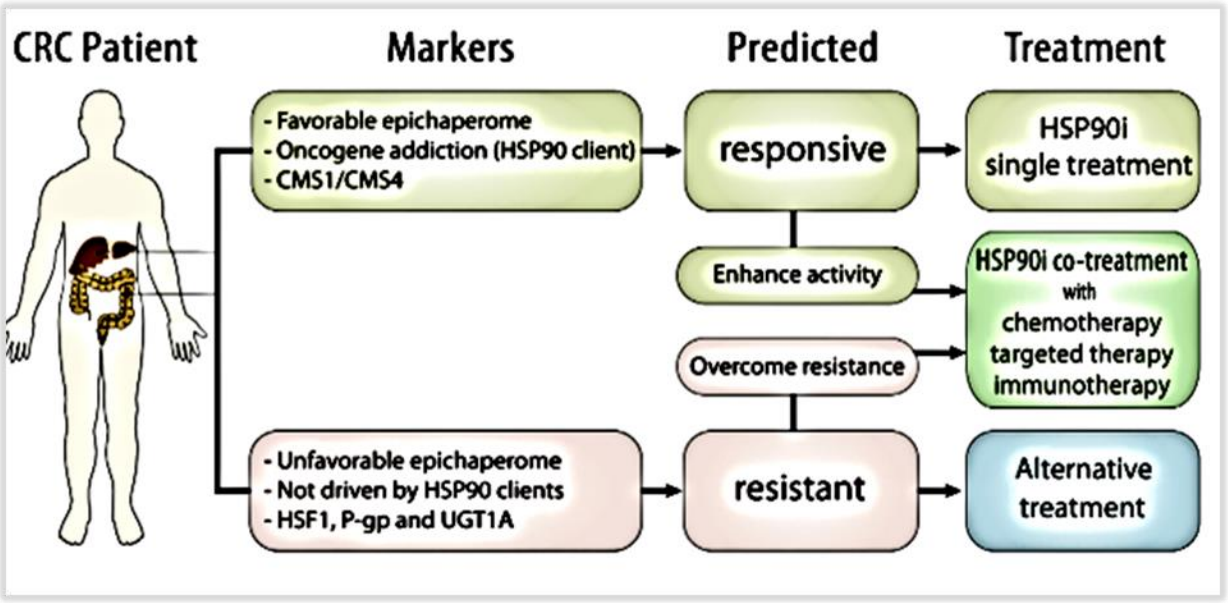

Figure No. 6: Stratification of CRC for HSP90 inhibition. Indicated are traits that predict sensitivity (light green) and resistance (red) to HSP90 inhibitors based on preclinical findings. HSP90 inhibitors are encouraged to combine with other drugs (dark green) to enhance their anticancer activity or bypass resistance, although, the clinical effectiveness remains to be further studied. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

1.9.5. Hsp90 as a Target of Anti-viral Drugs

It is now well established that Hsp90 is required for the correct folding, maturation, and assembly of many viral proteins and that the replication of many viruses is hypersensitive to Hsp90 inhibition.[26, 27] Viral client proteins of Hsp90 includes a large number of viral polymerases from both DNA and RNA viruses, such as DHBV (duck hepatitis virus), influenza virus A, HSV-1 (herpes simplex virus type 1) and FHV (Nodaviridae flock house virus). Hsp90 is also required for the activity of other viral proteins such as the large T antigen of SV40, a protease, and helicase form HCV (hepatitis C virus), as well as viral capsid proteins; see the recent review by Frydman and co-workers for further details.[26]In the case of capsid proteins, it is thought that Hsp90 is required as these clients need to be metastable, that is they must be sufficiently stable to withstand harsh extracellular conditions at the same time as needing to disassemble once inside cells. It has also216 S.E. Jackson already been shown that inhibition of Hsp90 with classic inhibitors such as geldanamycin and radicicol reduces viral activity and that they act broadly on a wide range of different viruses. In addition, and perhaps of crucial importance, is the emerging recognition that inhibition of

host Hsp90 results in anti-viral activity in which the virus cannot develop drug resistance.[28] The results of many studies highlight the potential of Hsp90 inhibitors as antiviral agents. [26, 27]

1.9.6. Hsp90 as a Therapeutic Target for Neurodegenerative Diseases

In recent years there has been increasing interest in Hsp90 as a target for several other disease states including many neurodegenerative disorders. Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and other dementias are characterized by the accumulation of soluble, oligomeric forms of specific proteins and aggregated sometimes amyloid-like insoluble fibrils.[29] In many cases, molecular chaperones including Hsp90 are found to co-localize in the aggregates either with the Alzheimer's-associated Ab plaques, the neurofibrillar tangles (NFTs) formed by phosphorylated tau, or in Parkinson's disease in the Lewy bodies formed by a-synuclein.[30,31] Proteomics techniques have begun to identify the changes in protein expression and the post-translational modifications in the brains of people affected by Alzheimer's disease and a recent study has identified that Hsp90 levels are significantly increased in the hippocampus of AD brains.[32]whilst other studies have shown that the levels of phosphorylated Hsp90 are reduced in PD brains.[33, 34]

1.9.7 Hsp90 as a Therapeutic Target against Protozoan Infections

In recent years there has been increasing interest in targeting Hsp90 in diseases other than cancer. [35]Hsp90 is known to affect important cellular transformations of intracellular protozoan parasites and human pathogens including Trypanosoma (strains of which are responsible for Chagas' disease and sleeping sickness), Leishmania (strains of which cause leishmaniasis), Toxoplasma, and Plasmodium (strains of which cause malaria). These parasites have evolved a relatively expanded or diverse complement of genes encoding molecular chaperones, presumably resulting from the fact that these parasites have to survive potentially hostile environments and their life cycles can involve multiple changes in environmental conditions including changes in temperature, pH, oxidative stress as well as desiccation.[36] For example, in L. major there are 17 copies of Hsp90 genes (many of which encode proteins with nearly identical sequences), and Leishmania also has a single copy of Grp94 which is thought to play a role in virulence.[37] In L. donovani it is estimated that Hsp90 constitutes some 3% of total protein content in the promastigotes stage.[38] There is also plenty of evidence for a plethora of Hsp90 cochaperones in Leishmania. [37] In Trypanosoma cruzi (the causative agent of Chagas' disease), there is a major cytosolic Hsp90 along with six

homologous genes, three genes encoding Grp94 homologs, and two genes encoding TRAP1 homologs. [37] Geldanamycin has been shown to cause growth arrest in T. cruzi; it is thought by preventing the maturation of proteins involved in epimastigote differentiation.[39] In mouse models of Trypanosoma evansi, treatment with inhibitors such as GA and 17-DMAG are effective in attenuating parasite growth and prolonging survival.[40]

2. SUMMARY

HSP90 plays a crucial role in maintaining oncogenic protein homeostasis. Heat-shock protein 90 inhibition offers great promise in the treatment of a wide variety of solid and hematological malignancies. Hsp90 can be viewed as a master regulator of signal transduction due to the wide array of signaling proteins and pathways that require the chaperone for optimal activity. It is well established that one of the cornerstones of malignant transformation is the dysregulation and persistent activation of a normal physiological process—cell cycle progression. Cancer is a disease of exceptional heterogeneity in which populations of tumor cells are remarkably adaptable and withstand an array of severe intrinsic and extrinsic stresses. These stresses reshape numerous cellular processes including metabolism, signaling, the folding and degradation of proteins (both wild type and mutant), and interactions with the microenvironment and immune system. Consequently, the protein folding machinery, and HSP90 in particular, has been identified as a promising therapeutic target for the treatment of cancer. Despite great success in generating potent and selective inhibitors of HSP90, however, the therapeutic potential of modulating this unique target has yet to be realized. Reflection on the disappointing performance of HSP90 inhibitors in the clinic raises questions about the choice of strategies adopted for their testing. Perhaps HSP90 inhibition is not the best way to kill cancer cells.

3. ACKNOWLEDGMENT

The authors are thankful to Sri. B. Premnath Reddy, Chairman, Management of Acharya Institutes and Principal Dr. Purnima Ashok, Acharya & BM Reddy College of Pharmacy, Bangalore for providing facilities for the successful completion of the study. I would like to express my love to loveable and respectable Babugee Mr. Samsulhak Miya and Aama Ms. Jaisul Nesha for taking all the pains and efforts to make this work an invaluable treasure.

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