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Potential Hsp90 Inhibitors: A Novel Target for Cancer Therapy

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Abstract

The uncontrolled growth of abnormal cells in the body is Cancer. With the rapid progression of molecular biology and genetics, emerging targets and therapeutics provides new opportunities for the prevention and treatment of several major disease systems. During drug discovery research many targets against cancer were also discovered. 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 (Figure 1). It also stabilizes a number of proteins required for tumor growth, which is why Hsp90 inhibitors are investigated as anti-cancer drugs. The function of Hsp90 includes assisting in protein folding, cell signaling, and tumor repression. Tumour-based Hsp90 has a significantly higher sensitivity than that in normal cells to inhibitors. Hsp90 activity inhibition in tumours leads to a suppression of cellular signaling in many different oncogenic pathways. Several inhibitors of Hsp90 are currently undergoing clinical evaluation and new agents with different mechanisms of action are continually being identified.

Keywords: Cancer; Target; HSP 90; Inhibitors; Isoform; Radicicol

Introduction

Cancer is the uncontrolled growth of abnormal cells in the body. Cancerous cells are also called malignant cells. There are several types of cancers depending on the organ they affect. However, they possess the same common properties of:

- Abnormal cell growth
- Capacity to invade other tissues
- Capacity to spread to distant organs via blood vessels or lymphatic channels (metastasis) [1,2].
- Causes of Cancer
- Physical agents (Radiations)
- Biological agents
- Chemical agents
- Genetic factors
- Mutations
- Diet and Habits
- Hormones and Drugs

Epidemiological factors

According to World Cancer Report from the International Agency for Research on cancer, cases of cancer doubled globally between 1975 and 2000, will double again by 2020, and will nearly triple by 2030. As of 2010, lung cancer is by far the most lethal type of cancer for men; breast cancer is the second-leading cause of cancer-related deaths for women (approximately 23 cases out of every 100,000 women), followed by colon and rectum cancer (15 out of every 100,000) [3].

Major Disadvantages of Anti-Cancer Agents

Toxic Side effects associated with them and Development of resistance [3].

Novel targets for cancer

With the rapid progression of molecular biology and genetics, emerging targets and therapeutics provides new opportunities for the prevention and treatment of several major disease systems. During drug discovery research many targets against cancer were also discovered [4,5]. The following are the novel targets for cancer:

Ras Kinase (Redundant acronym syndrome), Raf Kinase (Rapidly accelerated, fibrosarcoma), Her -2 inhibitors (Human Epidermal Growth Factor Receptor 2), Tyrosine kinases, JAK (Janus kinase inhibitor), AKT, HSP 90, MAK (mitogen-activated protein kinase).

HSP90

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 (Figure 1). It also stabilizes a number of proteins required for tumor growth, which is why Hsp90 inhibitors are investigated as anti-cancer drugs. Heat shock protein 90 (Hsp90) is one of the most common of the heat-related proteins. The "90" comes from the fact that it weighs roughly 90 kilo Daltons.

The function of Hsp90 includes assisting in protein folding, cell signaling, and tumor repression. This protein was first isolated by extracting proteins from stressed cells.

These cells were stressed by heating, dehydrating or by other means, all of which caused the cell's proteins to begin to denature [6-8].

HSP 90 Structure

Common features: The overall structure of Hsp90 is similar to that of other proteins in that it contains all of the common secondary structural elements (i.e., alpha helixes, beta pleated sheets, and random coils)(Figure 2). Hsp90 contains nine helices and eight anti-parallel beta

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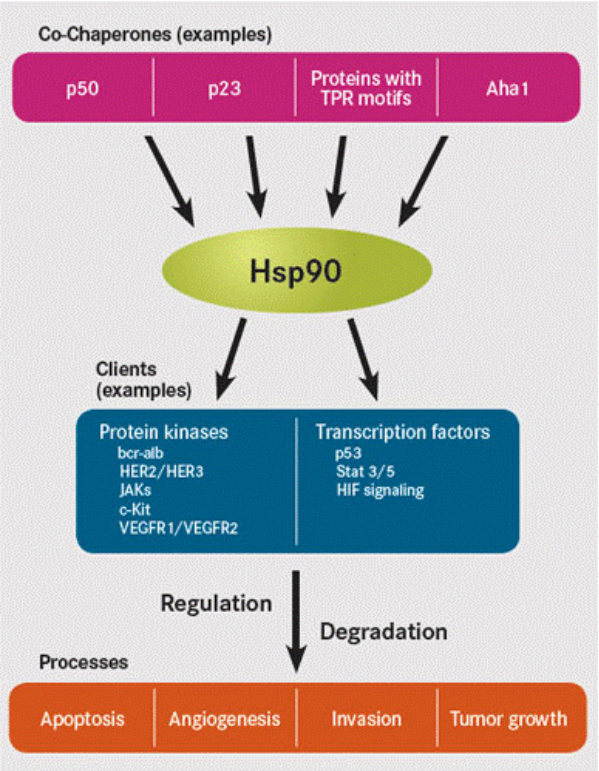

Figure 1: HSP90 Clients and the Multiple Hallmarks of Cancer.

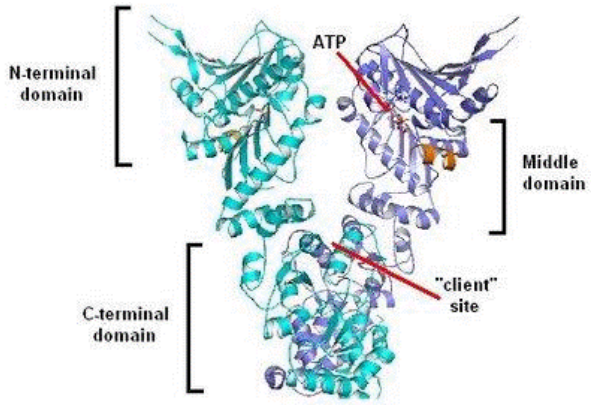

Figure 2: Structure of HSP90.

pleated sheets, which combine to form several alpha/beta sandwiches [8-10].

Domain structure: Hsp90 consists of four structural domains (Figure 3). A highly conserved N-terminal (NTD) domain of ~25 kDa, a "Charged linker" region that connects the N-terminus with the middle domain, a middle domain (MD) of ~ 40 kDa, a C-terminal domain (CTD) of ~ 12 kDa.

N-terminal domain: It contains an unusually shaped ATP binding cleft known as Bergerat fold, responsible for ATPase activity.

Middle domain: The middle domain is divided into three regions: A 3-layer α-β-α sandwich, a 3-turn α-helix and irregular loops, a 6-turn α-helix.The MD is involved in client protein binding.

C-terminal domain: The C-terminal domain possesses the binding site for co-chaperones.

Basic Difference between Normal Cells and Cancer Cells [11]

HSP 90 is over expressed in cancer cells. HSP 90 in cancer cells is associated with co chaperones (Figure 4). HSP 90 in normal cells is free.

Isoforms

There are five functional human genes encoding Hsp90 protein isoforms [12]. There are 12 human pseudo genes that encode additional Hsp90 isoforms that are not expressed as proteins (Table 1). A membrane-associated variant of cytosolic Hsp90, lacking an ATP-binding site, has recently been identified and was named Hsp90N.

HSP90 Inhibitors [13-15]

HSP 90 is the Heat shock protein. 90 denotes its molecular weight i.e., 90k daltons. The substance that which inhibits HSP 90 is HSP 90 inhibitor. As HSP 90 stabilizes proteins required for survival of cancer cells, its inhibition is of utmost impostance in cancer therapy. Natura HSP 90 products are Radicicol and Geldanamycin. The semisynthethic derivates include 17-N-Allylamino-17-demethoxygeldanamycin (17AAG). By far 23 HSP 90 inhibitors have been reported. Only few

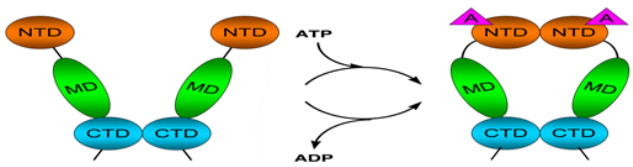

Figure 3: Domains of HSP90.

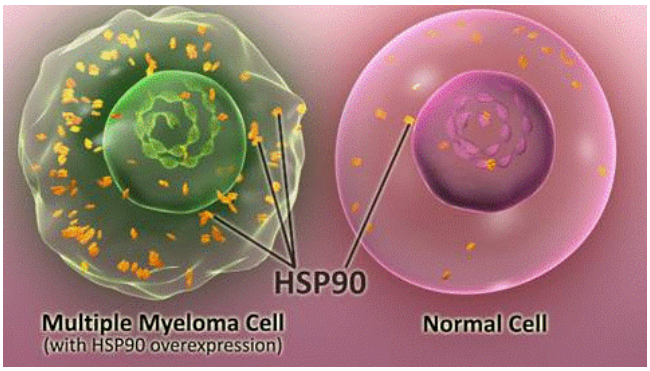

Figure 4: Difference between normal and cancer cells.

Family	Sub Cellular Location	Subfamily	Gene	Protein
HSP90A	cytosolic	HSP90AA (inducible)	HSP90AA1	Hsp90-α1
			HSP90AA2	Hsp90-α2
		HSP90AB (constitutively expressed)	HSP90AB1	Hsp90-β
HSP90B	endoplasmic reticulum		HSP90B1	Endoplasmin/ GRP-94
TRAP	mitochondrial		TRAP1	TNF Receptor-Associated Protein 1

Table 1: Isoforms of HSP90.

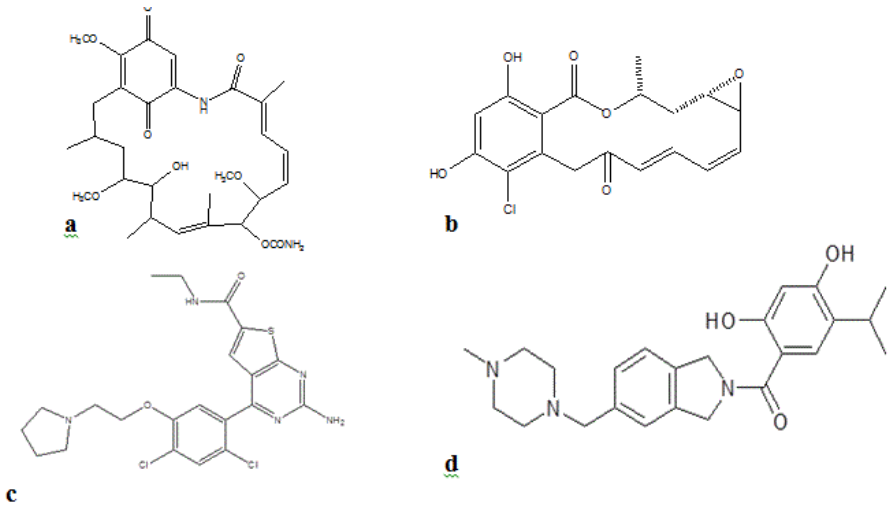

Figure 5: HSP90 inhibitors a. Radicicol b. Geldanamycin c. XL888 d. AT13387.

of their structures are derived eg. XL888 and AT13387 and are under clinical trials (Figure 5).

Conclusion

Tumour-based Hsp90 has a significantly higher sensitivity than that in normal cells to inhibitors. Hsp90 activity inhibition in tumors leads to a suppression of cellular signaling in many different oncogenic pathways. Several inhibitors of Hsp90 are currently undergoing clinical evaluation and new agents with different mechanisms of action are continually being identified which can definitely be the potential anti-cancer agents.

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