

# Heat Shock Protein as Emerging Oncologic Drug Targets

Lutfi Tutar<sup>1</sup>, Kübra Açıklan Coskun<sup>2</sup> and Yusuf Tutar<sup>2\*</sup>

<sup>1</sup>Department of Biology, Graduate School of Natural and Applied Sciences, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey

<sup>2</sup>Division of Biochemistry, Department of Basic Sciences, Faculty of Pharmacy, Sivas Cumhuriyet University, Turkey

\*Corresponding author: Yusuf Tutar, Division of Biochemistry, Department of Basic Sciences, Faculty of Pharmacy, Sivas Cumhuriyet University, Turkey, Tel: +90 3462191010; E-mail: ytutar@yahoo.com

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## Targeting Cellular Mechanics

Heat Shock Proteins (Hsps) form a network in human defense system and Hsps are universally conserved protein family among species. Proteins are key macromolecules in biochemical cascades and they must be correctly folded and stabilized for proper function. Hsps chaperone cellular proteins to maintain native substrate protein structure and behave as cellular mechanics to fix substrate proteins [1].

Chaperoning action of Hsps has been employed for drug designing studies. Inhibition of Hsp function lead cells to apoptosis and targeting Hsp with a proper inhibitor may lead impairment of Hsp function and this lead apoptosis of cells. The idea is especially useful for cancer cell destruction and studies focused on Hsp90 inhibitors since Hsp90 forms 1 to 2 percent of total cellular protein content.

## Heat Shock Proteins Basics

A classification of Hsps can be easily done by molecular size; Hsp27, Hsp40, Hsp60, Hsp70, Hsp90, Hsp100, small Hsps. Each Hsp has redundant isoforms, for example human Hsp90 has four isoforms and Hsp70 has 13 isoforms. Further Hsps are located at different parts of the cell i.e., cytosol, mitochondria, ER. And interestingly Hsps are expressed under constitutive and inductive conditions. Finally, Hsps cooperate and coordinate with the family members [2].

Hsps have several isoforms and different types. Different Hsps may form different complexes to serve for a range of biochemical functions but details of this network are still under investigation. Each compartment must be protected separately from stressors and this is probably the reason of Hsps existence in different cellular compartments. Heat, parasites, fungi, ischemia, infectious agents, malignancy, oxidative stress, and drugs are stressors and further cell protect itself from the effects of these factors by expressing Hsps for cell survival [1]. Under stress, cell induces more inductive Hsp form to help constitutively expressed Hsp.

Hsp induction indicates the presence of stress conditions in the metabolism and for this reason several metabolic diseases are associated with heat shock response. The aim of this paper is to review how can Hsps be employed for drug design studies?

Hsps are mechanics to fold the substrate proteins to their native state but this may be dangerous depending on the nature of the cell. If Hsps work properly in healthy cell, this is a desired outcome for biochemical processes. However, in cancer cells Hsps mediate survival and cause metastasis and drug designing studies focus on driving cancer cells to apoptosis-cancer cell destruction. And this approach is the ultimate target for Hsp dependent oncologic drug design.

Cancer cells metabolic rates are higher and thus, cancer cells employ more mechanics-Hsps to fold cellular proteins in shorter times. Inhibition of Hsps may perturb this mechanism and cellular substrate proteins may not be folded to their functional state. This leads a cancer cell to go to apoptosis and cancer cell death. For this purpose, several researchers design Hsp inhibitors. Designing a Hsp inhibitor in theory is a basic task but as mentioned above Hsps have complex network and inhibition of a specific Hsp may result of complementation. For example, inhibition of Hsp90 result by Hsp70 complementation. Inhibiting the right Hsp is a trial and error process. But luckily Hsp90 inhibition with a combinatorial treatment provides satisfactory outcomes. Geldanamycin is the template compound for Hsp90 inhibitor but researchers faced solubility problems with the compound. Over several years, researchers designed innovative derivatives of geldanamycin to make more soluble form [3].

## Current Designs

My lab designed Hsp90 inhibitors that inhibit both ATPase function of Hsp90 and substrate protein folding function of Hsp90. We further developed an Hsp70 inhibitor to perturb complementary function of the protein. The inhibitor not only inhibits Hsp70 substrate protein folding function but also binds to interface of protein-protein interaction sites. This interface inhibitor completely disrupts Hsps cooperative and coordinative function.

Currently, my lab determined a key miRNA and a pseudogene to completely kill cancer cell through the inhibition of these macromolecules. It should be noted that pseudogenes are expressed only at cancer cells. We further found out that cytosolic and mitochondrial Hsps involved in apoptosis are regulated by these miRNA and pseudogenes. Our efforts are to design an inhibitor to completely destroy Hsp network in cancerous cells and we may develop another drug for neurodegenerative diseases by employing similar strategy. Since Hsps are involved in substrate protein aggregation and fibril break, inhibition of certain Hsps may be a good strategy to prevent protein aggregation.

## References

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