

# Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

## Heat Shock Proteins: An Important Targets for Development of Next Generation Cancer Drugs

Aykut Özgür<sup>1</sup> and Yusuf Tutar<sup>2\*</sup>

<sup>1</sup>Department of Bioengineering, Faculty of Natural Sciences and Engineering, Gaziosmanpaşa University, Tokat, Turkey

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

### Short Commentary

Received date: 02/03/2016

Accepted date: 17/03/2016

Published date: 25/03/2016

#### \*For Correspondence

Yusuf Tutar, Department of Bioengineering, Faculty of Natural Sciences and Engineering, Gaziosmanpaşa University, Tokat, Turkey, Tel: +90 346 219 1010; Fax: +90 346 219 1634

**E-mail:** ytutar@outlook.com

**Keywords:** Heat shock protein, cancer, drug design, client proteins, protein folding

Cancer is the second most virulent disease in the world. Each year approximately 14 million new cancer cases are diagnosed around the world. Therefore, researchers have been focused on efficient target specific chemotherapeutics (microtubule, tyrosine kinase, EGFR, and VEGF inhibitors) for cancer for a long time <sup>[1]</sup>. For many years, heat shock proteins (Hsps) have been investigated in cancer progression and Hsps have become significant molecular target for next generation cancer drug design studies. Designing specific agents for different Hsps perturb different mechanisms in the cell for cancer treatment <sup>[2-4]</sup>.

Hsps are conserved protein family which has been identified among all organisms. Hsps are been classified on the basis of their molecular weight (small Hsps, Hsp40, Hsp60, Hsp70, Hsp90 and Hsp100). Hsps are produced in response to external and internal stress factors by cell. Hsps are essential biomolecules for cell survival and they play vital roles in protein maintenance processes: protein folding, prevention of protein aggregation, and stabilization of proteins <sup>[3,4]</sup>.

Cancer cells are exposed to highly oxidative stress conditions and their metabolic rates are faster compared to normal healthy cells. Under these cellular stress conditions, cancer cells need more Hsp macromolecules. Generally, Hsps are overexpressed in cancer cells. Hsp overexpression in tumor means either poor prognosis or higher resistance to anticancer treatment. Hsps block apoptotic factors and facilitate proper conformation of oncogenic client proteins. Especially, Hsp27, Hsp70, and Hsp90 are involved in oncogenic protein quality control processes in cancer progression <sup>[4-6]</sup>.

Hsp27 is a member of the small Hsp protein family and it is expressed in the nucleus, endoplasmic reticulum and cytosol. Under normal cellular conditions, Hsp27 works coordinately with Hsp40-Hsp70-Hsp100 chaperone complex. It provides resolubilization and refolding of the insoluble large protein aggregates. Hsp27 interacts with apoptotic signaling pathways in cancer cells and protects the cancer cells against apoptosis. Further, Hsp27 negatively regulates apoptotic factors (caspase 3 and 9, cytochrome c, Apaf-1 activation) and prevents DAXX translocation to the cell membrane <sup>[7,8]</sup>.

Hsp90 is a 90 kDa chaperone protein which is one of the most abundant proteins in eukaryotic cells and it is localized in cytosol, mitochondria, and endoplasmic reticulum. Oncogenic client proteins (transcriptional factors, tyrosine kinases, metastable/chimeric/mutated signaling proteins, cell cycle regulators) are participated in all stages of apoptosis, angiogenesis, cell proliferation, necrosis, metastases and invasion processes. They require native conformation and stability for proper function in these processes. Hsp90 is responsible for folding, activation and stabilization of oncogenic client proteins in cancer cells.

Thus, Hsp90 inhibition has become an essential therapeutic strategy for oncology. Several Hsp90 inhibitors are under clinical trial and most of them are ATP analog. Hsp90 has N-terminal domain which has ATPase activity. ATP hydrolysis energy provides conformational changes of Hsp90 for chaperone activity <sup>[4,9,10]</sup>.

Hsp70 is ubiquitously expressed and conserved chaperone protein family member. Hsp70 is one of the most important proteins folding machinery part in cell. Hsp70 forms a complex with Hsp40 and Hsp100 to generate protein folding and degradation of large protein aggregates processes <sup>[2]</sup>. Similar to Hsp90 chaperone activity, Hsp70 is essential biomolecules for cancer cell survival. It was reported that, inhibition of Hsp90 triggers Hsp70 expression and complements inhibited Hsp90 function. For this reason, Hsp70 expression decreases cell death and anti-tumoral activity induced by Hsp90 inhibition. With this knowledge on hand, inhibition of Hsp70 function and its interaction with other proteins have been important therapeutic aspect for cancer therapy <sup>[11-13]</sup>.

Currently, there are no FDA approved Hsps based chemotherapeutics in cancer treatment. However, pre-clinical and clinic phase studies are hopeful for novel Hsps based cancer drugs and may get approval from FDA soon.

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