

Current Drug Design Studies for Hsp70 in Oncological Applications

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Keywords: Hsp70; Hsp90; Cancer; Inhibitor; Drug design

Heat Shock Protein 70 (Hsp70) is a molecular chaperone having a major role in protein quality control under normal and stressful conditions. It prevents the aggregation, helps substrate protein folding, protein degradation, transportation, and regulation [1,2]. Hsp70 has two domains; substrate binding domain (SBD) and nucleotide binding domain (NBD). NBD binds to ATP and performs ATP hydrolysis in order to fold substrate proteins to their native structure. Native structure helps substrate protein to properly function. SBD contains hydrophobic amino acid residues, and this hydrophobic cavity helps unfolded substrate proteins to fold their native structure. Thus, exposed part of the folded proteins may not interact with each other and cause aggregation. The biological activity of Hsp70 family is based on ATP hydrolysis and hydrolysis rate is changed by some of the associated co-chaperone proteins [1,3,4].

Cancer cells are exposed to internal and external stress by cytokine attack, hypoxia due to inadequate blood supply, increased free radicals in the cellular milieu as a result, misfolded proteins accumulate in the cell [5,6].

HSPs play an especially important role in tumor formation and development. Cancer cells gain characteristic features as unlimited division ability, changing their local environment, and spreading to near and far tissues. Extracellular Hsp, Hsps released outside the cell, plays an essential role in spreading of cancer cells to distant tissues and environment. Further, Hsp also has a role inside cancer cell in order to stabilize the transcription factors and kinases during cell growth and Hsp also regulates cell cycle through p53 [6,7].

Ciocca et al. showed that the expression level of Hsp70 rises excessively in breast cancer cells. Later, same alteration was observed in colon, liver, prostate, esophagus, and cervix cancer. These findings suggested Hsp70 as potential biomarker for evaluating tumor stage, metastasis, and prognosis. It is reported that Hsp70 over-expression causes G₀/G₁ phase shortening and this leads increase in the number of human breast cancer cells [5,8].

Hsp70 can protect cancer cells from cell death, intrinsic and extrinsic apoptosis pathways by inhibiting pro-apoptotic factors. In the intrinsic apoptosis pathway, Hsp70 binds to Bcl-2-associated X protein (BAX), it prevents translocation in mitochondria. Hsp70 prevents recruitment of Apoptotic Protease Activating Factor 1 (Apaf-1) and procaspase-9 by interacting with mitochondrial membrane. In respect to the extrinsic pathway, Hsp70 inhibits death-inducing signaling complex (DISC) via binding to the death receptors DR4 and DR5. Upon entering to mitochondria, Hsp70 binds to several kinases (c-jun N-terminal kinase, p38 mitogen-activated protein kinase, stress-induced kinase) and blocks its function and inhibits apoptosis initiation signal. Furthermore, Hsp70 binds to apoptosis-inducing factor (AIF) and inhibits caspase-independent cell death [9-11].

As a result, Hsp70 which play a vital role in the maturation of proteins under physiological conditions can play an accelerating role in cancerous cells by inhibiting apoptosis. Since Hsp is one of the targets in oncological pathways, several researchers have been

working on inhibition mechanism of Hsp action. Several studies made especially on Hsp90 displayed satisfactory results but the major problem with Hsp family is its complementary function. Inhibition of Hsp90 triggers Hsp70 induction and Hsp70 may complement inhibited Hsp90 function. All Hsp types have isoforms for example human Hsp90 has four types, Hsp70 has 13 types. Each Hsp type may coordinate and cooperate with each other to perform specific functions in the cellular function. Therefore, inhibition studies should focus on specific pathways. Inhibiting certain proteins may not inhibit specific biochemical functions instead the mechanism of action for specific Hsp complex must be elucidated.

There are well known inhibitors in clinic applications which target Hsp90 ATPase domain; 17AAG and 17DMAG. Although Hsp70 identified as a potential drug target in cancer, apoptosis, and neurodegenerative disease, researchers did not give enough attention to Hsp70 inhibitors as Hsp90 inhibitors. Due to Hsp70 complementary function upon Hsp90 inhibition, Hsp70 inhibition studies accelerated. Only a few agents designed for Hsp70 inhibition; VER-155008 and PES which interacts with the ATPase domain and SBD respectively (Table 1). However, ATP binding cavity is hydrophilic and it is unlikely to develop a drug template from this interaction. Therefore, researchers are biased to hydrophobic SBD to design an efficient agent [12,13].

In our lab we designed and synthesized innovative inhibitors for Hsp complex system by targeting SBD of Hsp70. The designed inhibitors not only destroy function of each Hsp but also interact with Hsp interface to diminish protein-protein interaction. This model is useful in terms of preventing cooperating-coordinating interaction of proteins.

Further, the complex is investigated at gene level and miRNA and pseudogenes identified for control mechanism of Hsp dependent apoptosis. Our current effort is to determine all these key factors to completely inhibit apoptosis.

Inhibitor name	Target domain	Inhibited pathway
ATP Analog (VER-155008)	NBD	Apoptosis
Imidazoles	NBD	Apoptosis
MAL3-101	NBD	Exhibit Antimyeloma Effects
Methylene blue	NBD	Not defined
PES	SBD	Autophagy

Table 1: Hsp70 inhibitors.

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Received May 04, 2016; **Accepted** May 09, 2016; **Published** May 17, 2016

Citation: Coşkun KA, Tutar L, Tutar Y (2016) Current Drug Design Studies for Hsp70 in Oncological Applications. Cell Dev Biol 5: e140. doi:10.4172/2168-9296.1000e140

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