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Inhibition of Heat Shock Protein 70 and 90 (Hsp70 And Hsp90) in Target Spesific Cancer Treatment

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Hsp70 (70 kDa) and Hsp90 (90 kDa) are important members of the chaperone protein family. They are over-expressed in a wide range of tumor types (both solid tumors and hematological malignancies), and play essential roles in apoptosis, cell proliferation, metastases, angiogenesis, and invasion pathways in cancer cell metabolism. Hsp70 and Hsp90 provide stabilization; regulation and maintenance of oncogenic client proteins (Her-2, Cdk-4, Akt, Raf-1) thus promote cancer cell survival. Therefore, inhibition of Hsps was accepted potential therapeutic strategy for cancer for the last two decades [1,2].

Hsp90 is abundantly expressed in normal eukaryotic cells (1-2% of the whole cellular proteins). In cancer cells, Hsp90 expression is particularly higher than normal cells (4-6% of the whole cellular proteins). Geldanamycin is the first natural Hsp90 inhibitor which was isolated by Streptomyces hygroscopicus. Then, synthetic geldanamycin derivatives (17-AAG, 17-DMAG and IPI-504) were synthesized and their anticancer activities in clinical trials were evaluated. To date, numerous heterocyclic compounds have been designed, and different compounds are in various stages of clinical phase studies for Hsp90 inhibition [2]. Intensive investigations indicate that inhibition of Hsp90 is not enough by itself in cancer treatment. Inhibition of Hsp90 stimulates Hsp70 expression and Hsp70 complements Hsp90 chaperone activity. Hsp70 is abundantly expressed in human tumors, and protects cancer cells from apoptotic and necrotic factors. For this reason, Hsp70 expression decreases cell death and anticancer activity induced by Hsp90 inhibition [3]. Therefore, inhibition of Hsp70 and Hsp90 emerged as an important therapeutic strategy in cancer treatment.

Hsp70 and Hsp90 have conserved ATPase domain and their chaperone activities depend on ATP hydrolyses energy. Further, ATPase domains are also the binding site of many known inhibitors [1]. However, Hsp70 ATP binding site is not suitable for drug development and clinical trials since this site is deep and the nucleotide binds with polar interactions. Therefore, several inhibitors have been designed for Hsp70 substrate binding domain in recent years. Also, Hsp90 C terminal domain inhibitors have been designed as alternative Hsp90 inhibitors for effective cancer treatment [4].

Anticancer strategy effectiveness will be increased by simultaneous treatment of Hsp90 and Hsp70 inhibitors. Novel designs based on these critical interactions and application with other drugs will elucidate novel interaction mechanisms in the future studies.

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