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Editorial

Heat Shock Protein 90 c-Terminal Inhibitors in Cancer Treatment

Editorial

Heat shock protein 90 (Hsp90) is 90 kDa highly conserved dimeric chaperone protein in prokaryotic and eukaryotic cells and it is localized in different parts of the cell. Hsp90AA1 (inducible) and Hsp90AB1 (constitutive) are available in the cytosol; Grp94 and TRAP1 exist in endoplasmic reticulum and mitochondria; respectively. In unstressed cells, expression level of Hsp90 corresponds to 1-2% of total cellular protein, and Hsp90 is responsible for protein folding, maintenance and degradation of misfolded proteins, cell cycle control, and cellular signaling. Hsp90 is composed of three domains: N terminal domain (NTD), middle domain (MD), and C terminal domain (CTD). Hsp90 needs ATP hydrolysis energy to perform chaperone functions. NTD has ATP binding sites and ATP hydrolysis leads to large conformational changes for interaction between substrate proteins and Hsp90. CTD contains a conserved EEVD motif and the dimerization interface to regulate ATPase process and binding of co-chaperones (i.e. Hop, CHIP) in protein folding process [1-3].

In solid and hematological tumors, expression level of Hsp90 is increased about ten-fold compared to that of normal cells. Hsp90 play pivotal roles in apoptosis, angiogenesis, invasion, metastases, and cell differentiation in tumoregenesis. Hsp90 is mainly involved in maintaining, folding, and stability of oncogenic client proteins, including transmembrane tyrosine kinases, cell cycle regulators, transcription factors, steroid receptors, metastable/chimeric/mutated signaling proteins, in oncogenic signaling pathways. Hsp90 is essential for cancer cell survival and tumor progression pathways, therefore; Hsp90 inhibition has been remarkable anti-cancer drug target in oncology [2-4].

Disruption of Hsp90 ATPase function is the main strategy to develop Hsp90 inhibitors. Many natural and synthetic compounds have been tested as Hsp90 NTD inhibitors up till now and currently approximately twenty compounds (i.e. 17-AAG, 17-DMAG, IPI-504, AUY922, STA-9090, and BIIB021) are under clinical trials for cancer treatment. Clinical trial reports indicated that many of the compounds have hepatotoxic effects for normal healthy cells. Also, these ATPase blockers show unspecific interactions with other ATPase proteins in metabolism. All these negative features have led to develop new Hsp90 inhibition strategies. Recently, CTD inhibitors have been designed and their anti-cancer potentials have been evaluated in literature and clinical trials. CTD inhibitors perturb dimerization of Hsp90 and disrupt proper folding of oncogenic client proteins. Currently, natural CTD inhibitor, (-)-EGCG (green tea extract), is under clinical trials, and its anti-cancer properties have been evaluated in human lung, prostate, and breast cancer patients [2,5,6].

Coumarine (2H-1-benzopyran-2-ones) is benzopyrone class compounds and its derivatives are shown a wide spectrum of biological activity. Particularly, coumarine derivative compounds (novobiocin, coumermycin A1, KU135, and chlorobiocin) have an affinity for binding to the CTD and disrupting Hsp90 dimerization. Consequently, these compounds inhibit proper folding of oncogenic client proteins and cause elimination of the substrate proteins via ubiquitination-proteasome pathway [6,7]. In an effort, we designed and synthesized novel thiazolyl coumarine derivatives, and their anti-cancer activities were tested on human colon (DLD-1) and liver (HepG2) cancer cell lines. According to the biochemical and in-silico experiments, thiazolyl coumarine derivative compounds inhibited Hsp90 chaperone functions through disrupting CTD conformational change. Furthermore, these compounds disrupted interaction between Hsp90, Hop, Hsp40, and Hsp70 proteins in cancer cells. Briefly, thiazolyl coumarine derivatives are effective and potential Hsp90 CTD inhibitors as anti-cancer agents [6]. CTD inhibition strategy and increased biochemical and pharmacological knowledge about Hsp90 provide significant opportunities for anti-cancer drug development.

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