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Heat Shock Proteins, microRNAs, and Drug Design Studies in Medicinal Chemistry

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Heat shock proteins (Hsps) are highly conserved chaperone protein family which is responsible for proper folding of newly synthesized and misfolded proteins, cellular signaling, and prevention of protein aggregation. Hsps consist of six major members: small Hsps (<30 kDa), Hsp40 (40 kDa), Hsp60 (60 kDa), Hsp70 (70 kDa), Hsp90 (90 kDa), and Hsp100 (100 kDa). Hsps are found at different parts of the cell (mitochondria, endoplasmic reticulum, cytosol) and their expression level is increased under cellular stress conditions (i.e. malignancy, infection, heavy metals, heat, hypoxia, and oxidative stress). Therefore, expression of high levels of Hsps is related with disease's pathogenesis [1-3]. In our laboratory, we investigate potential roles of Hsps in tumoregenesis and pathogenesis of infection diseases.

Toxoplasmosis is an important infection disease caused by the protozoan *Toxoplasma gondii*. *T. gondii* is an ubiquitous obligate intracellular parasite and important member of the apicomplexan phylum/family. *T. gondii* infects one out of three people in the world, and this infection is observed at immunocompromised individuals such as AIDS patients and pregnant women. These individuals may become seriously ill and the parasite can occasionally cause death. Furthermore, toxoplasmosis causes morbidity and mortality when transmitted during pregnancy. It can cause inflammation of the brain, neurologic diseases, and it also affects the heart, liver, inner ears, and eyes. In humans, the life cycle of *T. gondii* has two stages: tachyzoite and bradyzoite. Tachyzoite is infective form of *T. gondii* and causes toxoplasmosis. In later stage of infection, tachyzoites are converted to bradyzoites, and can remain latent in the human tissues [4-6]. Our studies aim to characterize and investigate *T. gondii* Hsps to understand *T. gondii* survival in the host organism and develop new therapeutic strategies against toxoplasmosis. In an effort, Hsp40, Hsp70, and Hsp100 isolated from infective *T. gondii* RH strain, and the Hsps expressions are increased during conversion from tachyzoites to bradyzoites. Moreover, inhibition of Hsps suppresses bradyzoite development in host cell [7,8].

Hsps play essential roles in all stages of tumoregenesis. Proteins expose to poor conditions and cellular stresses (oxidative stress, hypoxia) in cancer cells. Hsps are overexpressed in tumors to protect three dimensional structures of oncogenic proteins and provide cellular hemostasis [9,10]. Especially, Hsp90 is involved in correct folding, stabilization, and activation of oncogenic proteins, thus apoptosis, angiogenesis, cell proliferation, metastases, and invasion pathways need Hsp90 chaperone activity. Hsp90 is one of the most expressed proteins in normal cells, and its expression can increase up to 10-fold in tumors. Therefore, inhibition of Hsp90 has been significant therapeutic perspective in cancer treatment [2,11,12]. In our study, we synthesized novel thiazolyl coumarine derivatives, and their anti-cancer activities were tested on human liver and colon cancer cell lines. Coumarine is benzopyrone class compounds and especially demonstrates anticancer and antimicrobial activity. Biochemical and *in-silico* experiments showed that, thiazolyl coumarine derivative compounds inhibited Hsp90 chaperone functions and have important potential to develop new target specific anticancer drugs [13].

Oncogenic kinase enzymes, estrogen receptor alpha (ER-α) and heme oxygenase have been extensively investigated in target specific cancer drug design studies by my research group. Kinase enzymes, including serine-threonine protein kinases, cyclin-dependent kinases, c-Jun N-terminal kinases, are overexpressed in tumor cells and participate in oncogenic signaling pathways [14]. In our recent works, we synthesized novel acyl thiourea derivatives containing pyrazole ring compounds and determined their anticancer activities on leukemia, colon, liver, breast, and bone cancer cell line as potential Aurora kinase inhibitors [15,16]. ER-α is an important biological marker around 70% of breast cancer cases. ER-α actives oncogenic signaling pathways and stimulates proliferation of breast tumors. In order to interrupt breast tumorgenesis, blocking of ER-α is accepted common treatment and preventive strategy, and FDA approved ER-α inhibitors are applied in ER-α positive breast cancer patient [17]. Novel alnustone (a nonphenolic diarylheptanoid) derivative compounds were designed as an ER-α inhibitor by our research group. Anticancer activities of compounds were determined on human ER-α positive invasive ductal breast cancer cell line (MCF-7). According to the experimental results, these compounds exhibited both protective and therapeutic activity by blocking tumorgenesis of human breast cancer cells [18]. Heme oxygenases are signaling molecules which catalyze heme degradation and CO release. Especially heme oxygenase-1 has cytoprotective properties against cellular stress factors (hypoxia, hydrogen peroxide, and reactive oxygen species). Heme oxygenase-1 inhibits angiogenesis and triggers apoptosis in cancer cells. Therefore, CO-releasing molecules (CO-RMs) have been designed and synthesized for treatment of cancer and infection diseases in the literature. CORMs supply CO for cancer cells and inhibit several apoptosis and angiogenesis related oncogenic protein, matrix metalloproteinase-9 (MMP9) [19,20]. We synthesized novel manganese containing CORMs, and now their anticancer activities are being tested on human breast cancer cell lines.

MicroRNAs (miRNAs) are short (18-22 nucleotide long) non-coding RNA molecules which are involved in gene regulation in normal and cancer cells (http://www.mirbase.org/). Human tumors are regulated by miRNA expression levels, claimed as oncogene and/or tumor suppressor. miRNAs defined as major regulators of coding genes in genome and are new agents that is employed in diagnosis, prognosis and gene targeting at therapeutic biomarkers in pharmacology. miRNAs inhibit tumoregenesis and play key roles in regulation of cancer metastasis. Furthermore, miRNAs are essential in

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biological processes such as cell progression, differentiation, growth, and apoptosis. Therefore, there is a growing interest in anti-cancer therapeutic research at recent years [21-23]. My research group focuses on the relationship between miRNA expression and cancer prognosis in human cancer cell lines. Moreover; the effect of miRNA expression on Hsps regulation is investigated in tumorgenesis. In our previous paper, relationships between HSP isoforms with miRNAs were determined on NCI-60 breast cancer cell lines by using Cell Miner analysis tool [24].

Research at molecular level promotes innovative outcomes and my research is focused on biochemical pathways to elucidate molecular mechanisms.

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