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Celastrol Mediated Hsp90 Protein Inhibition in Cancer

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Letter to Editor

In 2012, according to the globocan data 14.2 million new cases of cancer and 8.2 million cancer associated deaths had been reported. Lack of knowledge in cancer biology has major role for such disaster which increasing the enthusiasm to come up with promising anti-cancer therapy [1]. Discovery of new drug targets in cancer cell urgently required to reduce the mortality and to increase survival rate. The aberrant expression of Heat shock protein (Hsp) 90 has been correlated in all the cancer processes such as cell cycle arrest, angiogenesis, and metastasis [2-8]. So, identification of Hsp90 function in tumor cell may really be helpful which could serve as prognosis biomarker. The Hsp90 is a major molecular chaperone abundantly expressed in all cell types and plays pivotal role in correct folding and functionality of client proteins [9,10].

Hsp90 is up-regulated in response to cellular stress imposed by heat, hypoxia and nutrient deprivation, which is known to be commonly associated with the tumor microenvironment (TME). Recently, an elevated Hsp90 expression was determined in the breast cancer in contrast to non-cancerous tissues [10,11]. Similarly, profiles of 4,000 breast cancer patients from 23 public gene expression databases have shown an increased levels of Hsp90 proteins and poor survival rate of patients [12]. In addition, increased Hsp90 expression has also been analyzed in other malignancies including lung cancer, melanoma, leukemia and colon cancer [2,3]. Several Hsp90 inhibitors such as geldanamycin derivative 17-allylamino-17-demethoxygeldanamycin (17AAG) exhibited anti-neoplastic efficacy in many preclinical models like gastrointestinal carcinomas [6].

Even Hsp90 inhibitors have been progressed to phase I/II clinical trial [13]. Promising result of Hsp90 inhibitors has been noticed in TKI (tyrosine kinase inhibitor) resistance , EGFR (epidermal growth factor receptor), NSCLC (non-small cell lung carcinoma), during clinical trials [14]. Besides the synthetic Hsp90 inhibitors, phytochemicals are also proved beneficial against several human diseases including diabetes, cardiovascular, neurodegenerative, and cancers [15-18]. For instance, celastrol isolated from the root extract of Trypterigium wilfordii (Thunder God Vine) is a pentacyclic triterpenoid and well-studied for its multiple pharmacological functions by modulating a variety of cellular signalling pathways. Specially, celastrol's anti-cancer potential via Hsp90 inhibition has been widely studied. For example, celastrol can regulate many transcription factors (TFs) by altering Hsp90/TFs and Hsp 90/Hop, Hsp90/Cdc37 interaction found in MCF-7, Hep G2, and Tamm-Horsfall protein 1 (THP-1) [19].

Celastrol binds to C-terminal and N-terminal domain of Hsp90 domain and allosterically regulate its chaperone activity and disrupt Hsp90-cdc37 involute [20,21]. Celastrol inhibited the ATP-binding activity of Hsp90 which has already been known as target for anticancer therapy. Further, celastrol arrest U937 cell in G0/G1 phase in a dose-dependent manner by inhibiting Hsp90 governed ATPase activity along with elevation of Hsp70 levels, reduction in cyclin D1, Cdk4 and Cdk6 levels, and disruption of Hsp90/Cdc37/Cdk4 involute [4,5]. Treatment of NCI-H460 lung cancer cell line with celastrol showed increased radio-sensitivity due to decreased levels of Hsp90 clients such as EGFR, ErbB2, and survivin, and increased p53 expression [6].

In addition, the partly inhibitory effect of celastrol on HiF-1α protein due to suppression of Hsp90 activity was also determined [7]. Celastrol also inhibited proteosomes in cervical cancer cells (HeLa cells), activates caspases and degraded lung cancer cells (Hsp90 in H1650 and H1975) [8,22-32]. Thus, the discussed experimental data is showing the role of celastrol in Hsp90 inhibition and tumor suppression. Therefore, we emphasize the utilization of celastrol and Hsp90 mediated approaches in further clinical studies by using animal models as well human subjects.

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