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17-Allylamino-17-demethoxygeldanamycin loaded PCL/PEG nanofibrous scaffold for effective growth inhibition of T47D breast cancer cells

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ABSTRACT

The study describes the fabrication of an implantable nanofibrous scaffold loaded with 17AAG as a heat shock protein 90 (Hsp90) inhibitor for possible application in breast cancer therapy. In order to, 17AAG loaded PCL/PEG nanofibers (NFs) were prepared by electrospinning technique and their chemical and physical properties studied by FTIR and FESEM. To assess cytotoxicity of 17AAG loaded PCL/PEG NFs and free 17AAG on T47D cancer cells as *in vitro* model of breast cancer, MTT assay was performed. The mRNA expression level of Hsp90 and telomerase activity in treated cells with 17AAG loaded PCL/PEG NFs also were investigated using real-time PCR (RT-PCR) and TRAP method, respectively. MTT method indicated which loading of the 17AAG into PCL/PEG NFs increased effectively cytotoxicity against T47D cells. This result was correlated with significant decrease of telomerase activity and mRNA expression level in treated cells with 17AAG loaded PCL/PEG NFs compared to free 17AAG. In conclusion, the results confirmed which 17AAG loaded PCL/PEG NFs are further effective compared with free 17AAG on T47D breast cancer cells through reduction of telomerase activity and Hsp90 mRNA expression level. Therefore, 17AAG loaded NFs might be a superior device to remove of residual breast cancerous cells and prevent locally cancer recurrence.

1. Introduction

Local breast cancer recurrence arise in 3–15% of patients during 5–10 years after breast-conserving surgery [1]. Local recurrence is as a result of residual cancer cells in the breast at the time of primary tumor resection surgery or de novo tumor formation in the breast [2]. Hence, the preparation and advancement of agents which had ability to remove residual cancerous cells and prevent local cancer recurrence, is a substantial need [3].

The Hsp90, a plentiful molecular chaperone in eukaryote cells, has key roles in cellular processes including the organization and maturation of client proteins in a multicomponent complex of co-chaperone proteins regulated through the binding and hydrolysis of ATP [4,5].

The Hsp90 expression and its ATPase activity are increased in breast cancer cells, as well as, normal chaperoning functions of Hsp90 can be used at the time tumorigenesis to promote malignant progression, suggesting a key role for Hsp90 in maintaining a transformed cellular phenotype and make it a potential target for breast cancer treatment [6,7].

Telomerase is a cellular multi-component ribonucleoprotein enzyme [8,9]. The function of telomerase is synthesizing and elongating of telomeric DNA in end of linear chromosomes which known as telomeres [10].

Both the main component of human active telomerase include a the template RNA component hTR, for reverse transcription of telomeric repeats, and a the catalytic protein component hTERT, as reverse transcriptase are essential for telomerase activity [11,12]. Whereas the hTR is expressed in both normal and cancer cells, hTERT expression is limited to cancer cells with active telomerase. Therefore, hTERT has a rate-limiting effect on enzymatic activity of telomerase (13.14).

Hsp90 and its co-chaperone p23 are involved in the proper telomerase assembly in normal cells through binding to hTERT, and

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