Combination of Cold Atmospheric Plasma and Nanoparticles Drug Delivery toward More Efficient Breast Cancer Therapy

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Statement of Purpose: Cold atmospheric plasma (CAP) is an ionized non-thermal gas mixture which is composed of various reactive oxygen species, reactive nitrogen species, and UV photons, etc. It has drawn tremendous interest in a variety of biomedical applications including cancer treatments. Meanwhile, delivery of anti-cancer agents using novel nanoparticle carriers has presented intrinsic advantages than direct drug administration. In this study, we combine the two advanced techniques together in order to obtain a more efficient breast cancer dual treatment method. For this purpose, we fabricated a novel core-shell nanoparticles drug delivery system and integrated it with CAP to explore their synergistic effects on inhibiting breast cancer cell functions.

Methods: The core-shell nanoparticles were synthesized via an electrospraying technique and imaged by SEM (Scaning Electron Microscope) and TEM (Transmission Electron Microscope). Poly(lactic-co-glycolic) acid (PLGA) was selected as shell to incorporate anticancer drug 5-Fu (5-Fluorouracil) within the nanoparticles. Metastatic MDA-MB-231 breast cancer cells were selected to investigate the anti-cancer effect of nanoparticles and CAP. Human bone marrow-derived stem cell (MSC) was used to test the cytotoxicity of nanoparticles to healthy cells. The influence of CAP treatment on MDA-MB-231 gene expression was detected using RT-PCR (real time-polymerase chain reaction).

Results: SEM and TEM micrographs (Figure 1) showed the nanoparticles have homogenous size distribution with a diameter of ~150 nm. The 5-Fu loading efficacy is 24.1%, and the encapsulation efficacy is 64.27%. Cell studies showed the 5-Fu encapsulated nanoparticles can great inhibit breast cancer cell growth and present the dependence of dosage in the concentration range of 25 μg/mL to 200 μg /mL (Figure 2). Whereas, MSCs can keep a cell viability of more than 70% even though undergoing a 200 μg/mL nanoparticles treatment. RT-PCR results revealed CAP treatment down-regulated the metastasis related genes (VEGF, MMP9, MMP2, MTDH) expression (Figure 3). Especially, 60s CAP treatment has a greater inhibition in these gene expression. The combination of drug-loaded nanoparticles and CAP can synergistically inhibit breast cancer cells growth for 24 hour culture when compared to each single treatment (Figure 4).

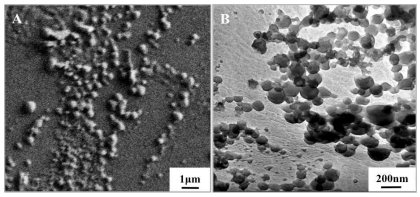

Figure 1. Morphology analysis of drug loaded PLGA nanoparticles SEM (A) and TEM (B) micrographs.

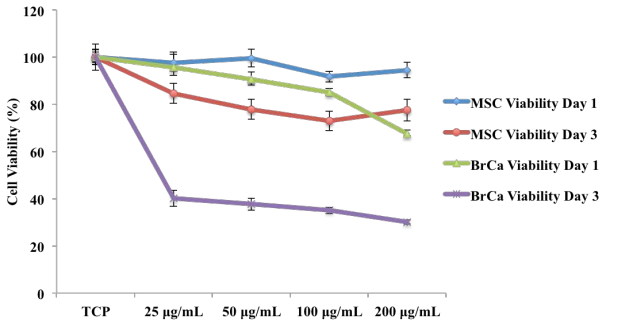

Figure 2. MSC and MDA-MB-231 cell responses to media containing various concentration drug loaded nanoparticles within 1 day and 3 days. TCP (tissue culture plate) is the control group that cells were in media only. Data are mean ± standard error of the mean, n=9.

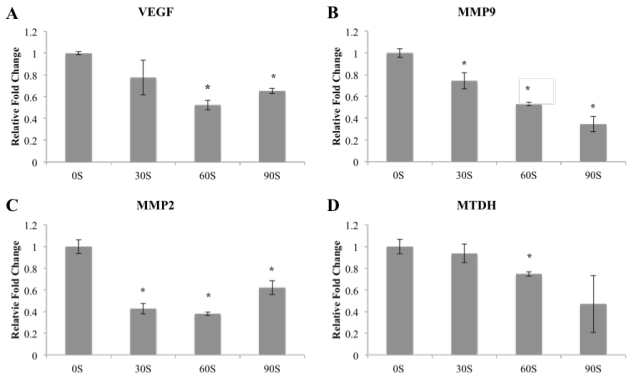

Figure 3. MDA-MB-231 gene expression when treating with different time CAP. Data are mean ± standard error of the mean, n=9, *p<0.05 when compared to 0s group (without CAP treatment).

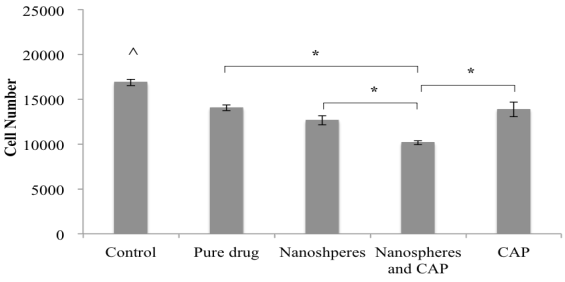

Figure 4. MDA-MB-231 cell growth within 24 h under varying conditions. CAP treatment was 60s. Data are mean ± standard error of the mean, n=9, *p<0.05; in addition, ^p<0.05 when compared to all other experimental groups with CAP or nanoparticles.

Conclusions: The combination of novel CAP and core shell nano drug delivery system greatly inhibits the breast cancer cell growth and metastatic gene expression, thus provides a promising strategy for treating breast cancer.

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