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Enhancement of Radiosensitization by Aptamer 5TR1-Functionalized AgNCs for Triple-Negative Breast Cancer

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Abstract : Triple-negative breast cancer (TNBC) is the most malignant subtype of breast cancer with a poor prognosis, and radiotherapy is one of the main treatment methods. However, due to the obvious resistance of tumor cells to radiotherapy, high dose of ionizing radiation is required during radiotherapy, which causes serious damage to normal tissues near the tumor. Therefore, how to improve radiotherapy resistance and enhance the specific killing of tumor cells by radiation is a hot issue that needs to be solved in clinic. Recent studies have shown that silver-based nanoparticles have strong radiosensitization, and silver nanoclusters (AgNCs) also provide a broad prospect for tumor targeted radiosensitization therapy due to their ultra-small size, low toxicity or non-toxicity, self-fluorescence and strong photostability. Aptamer 5TR1 is a 25-base oligonucleotide aptamer that can specifically bind to mucin-1 highly expressed on the membrane surface of TNBC 4T1 cells, and can be used as a highly efficient tumor targeting molecule. In this study, AgNCs were synthesized by DNA template based on 5TR1 aptamer (NC-T5-5TR1), and its role as a targeted radiosensitizer in TNBC radiotherapy was investigated. The optimal DNA template was first screened by fluorescence emission spectroscopy, and NC-T5-5TR1 was prepared. NC-T5-5TR1 was characterized by transmission electron microscopy, ultraviolet-visible spectroscopy and dynamic light scattering. The inhibitory effect of NC-T5-5TR1 on cell activity was evaluated using the MTT method. Laser confocal microscopy was employed to observe NC-T5-5TR1 targeting 4T1 cells and verify its self-fluorescence characteristics. The uptake of NC-T5-5TR1 by 4T1 cells was observed by dark-field imaging, and the uptake peak was evaluated by inductively coupled plasma mass spectrometry. The radiation sensitization effect of NC-T5-5TR1 was evaluated through cell cloning and in vivo anti-tumor experiments. Annexin V-FITC/PI double staining flow cytometry was utilized to detect the impact of nanomaterials combined with radiotherapy on apoptosis. The results demonstrated that the particle size of NC-T5-5TR1 is about 2 nm, and the UV-visible absorption spectrum detection verifies the successful construction of NC-T5-5TR1, and it shows good dispersion. NC-T5-5TR1 significantly inhibited the activity of 4T1 cells and effectively targeted and fluoresced within 4T1 cells. The uptake of NC-T5-5TR1 reached its peak at 3 h in the tumor area. Compared with AgNCs without aptamer modification, NC-T5-5TR1 exhibited superior radiation sensitization, and combined radiotherapy significantly inhibited the activity of 4T1 cells and tumor growth in 4T1-bearing mice. The apoptosis level of NC-T5-5TR1 combined with radiation was significantly increased. These findings provide important theoretical and experimental support for NC-T5-5TR1 as a radiation sensitizer for TNBC.

Keywords : 5TR1 aptamer, silver nanoclusters, radio sensitization, triple-negative breast cancer
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