Enhanced Anti-tumor Efficacy of Sonosensitized Drug Loaded Nanocomposites against Metastatic Breast Tumors

Pengying Wu[1], Shifang Guo[1], Xiaoyang Qiao[1], Ayache Bouakaz[2], Yujin Zong[1], Mingxi Wan[1]*
1 Key Laboratory of Biomedical Information Engineering of Ministry of Education, and Department of Biomedical Engineering, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an 710049, PR China.
2 UMR 1253, iBrain, Université de Tours, Inserm, Tours, France

Background, Motivation and Objective

The motivation of the work is to provide a synergistic effect to chemotherapy loaded nanoparticles combined with ultrasound (US) application through sonosensitizers and targeting. Hence, the objective is to develop a nanoparticle complex containing anticancer drug, a targeting agent and a sonosensitizer compound and to evaluate the therapeutic efficacy of this complex in a primary breast tumor and lung metastases lesions.

Statement of Contribution/Methods

We designed and fabricated targeted nanoparticles (NPs) composed of a dendrimer (PCH) core, containing a fluorochrome indocyanine green (ICG) acting as a sonosensitizer, an anti-tumor drug doxorubicin (Dox) and Hyaluronic acid (HA) for targeting capabilities (Fig. A, B). HA is incorporated to target CD44 marker overexpressed in mouse 4T1 breast tumor cell. Antitumor efficacy of the nanocomplex was evaluated in a mouse model of lung metastasis from 4T1 breast tumor. US were applied using 1.2 MHz during 3 min at 3 W output power.

Results/Discussion

We have prepared HPCID of CD44 targeted NPs with an average size of about 12 nm. Results (Fig. C) demonstrate an evident synergistic effect with the presence of the sonosensitizer (ICG). Indeed, breast tumor growth was significantly reduced using HPCID NPs in comparison to NPs without ICG (HPCD) (n = 8). This is confirmed in the confocal images (Fig. D) showing an enhanced concentration and distribution of Dox in tumor section in HPCID+US group compared to HPCD group+US. The enhanced permeability is ascribed to an increased ROS generation in the tumor section as depicted in Fig. E. Finally, application of US on the primary tumor showed a significant reduction of lung metastases when combined with HPCID NPs in comparison to HPCD NPs group (Fig. F). Taken together, HPCID NPs show great promise against breast cancer and metastasis progression.

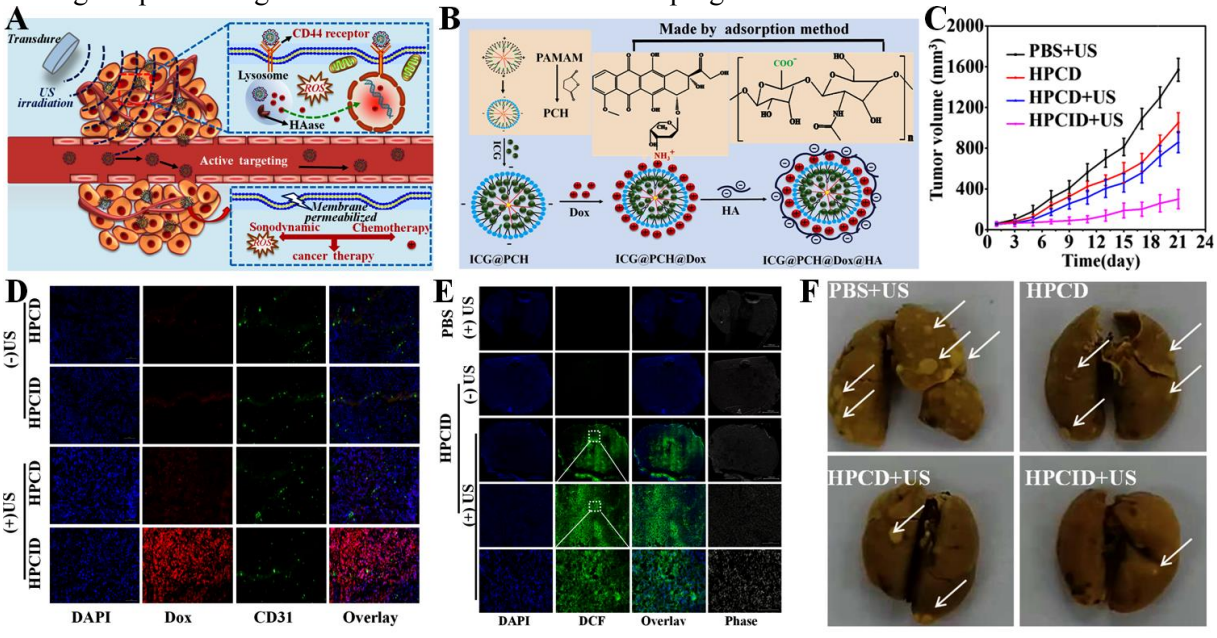

Fig.1. (A)Schematic illustration of sonochemotherapy of HPCID nanoparticles.(B) Synthesis of nanocomposite with Dox and HA targeting and ICG. (C) Tumor volumes growth for different groups PBS+US, HPCD; HPCD+US; HPCID+US. (D) Confocal images of tumor sections for different groups. (E) Confocal imaging of tumor section showing ROS generation (F) Pulmonary metastasis image of different groups PBS+US, HPCD; HPCD+US; HPCID+US.