ROS-Responsive Blended Nanoparticles: Cascade-amplifying synergistic effects of chemo-sonodynamic therapy with on-demand boosted drug release

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Background, Motivation and Objective

Drug loaded nanoparticles in combination with US have shown potential for the treatment of primary and metastatic tumors where the drug release is induced through a direct mechanical or thermal action of US. The objective of this study is to develop drug loaded nanoparticles with active release to achieve an enhanced synergistic effect with US.

Statement of Contribution/Methods

ROS-responsive DSPE nanoparticles IR780/PTL-NPs were designed. They consisted of a lipid core and ROS-cleave thioketal linkers (TL) to boost drug release after US activation. PEGylation of the nanoparticles was associated with TL-modified paclitaxel (PTX-TL) to form the block copolymer. In addition, IR780, a ROS responsive compound as it produces ROS upon US application, was mixed to the block copolymer PTX-TL-PEG_{1K}-NH_2 with DSPE-PEG-NH_2 (Fig. A). Therapeutic efficacy of IR780/PTL-NPs was evaluated both *in vitro* and *in vivo* in a xenograft glioblastoma mice model. US was applied at 1 MHz during 3 min at output electric power of 4W.

Results/Discussion

In vitro results showed a 3-fold increase in drug release from NPs when associated with IR780compared to without IR780 (Fig. Ba). Association of the NPs with a specific ROS scavenger NaN3 induced a release profile (Fig. Bb) similar to the NPs without IR780. TEM images confirmed the significant release from the IR780/PTL-NPs in comparison to NPs without IR780(Fig. Bc,d).Therapeutic efficacy study showed a significant tumor volume reduction in IR780/PTL-NPs group in comparison to PTL-NPs group (Fig. C). This is confirmed though measurements of tumor weight (Fig. D). In addition, body weight of the animals indicated no undesirable effects as it did not change throughout treatment (Fig. E). The designed IR780/PTL-NPs provide amplified synergistic effects with a controlled release of drugs both spatially and temporally with a high therapeutic benefit.

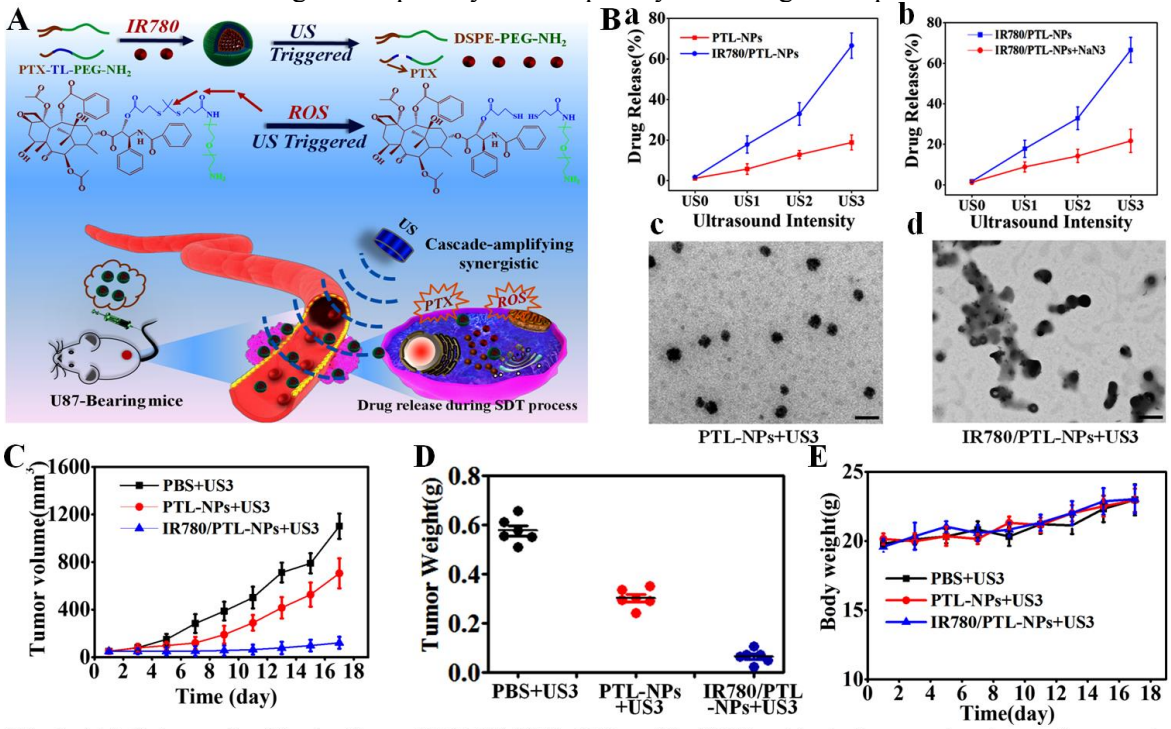

Fig.1 (A) Schematic illustration of IR780/PTL-NPs with SDT-activated cascade chemotherapy to synergistically treat cancer cell. (B)The cumulative amount of PTX released from IR780/PTL-NPs following US irradiation(a, b) and morphological changes of PTL-NPs and IR780/PTL-NPs after US3 irradiation (c,d). Scale bar is 200 nm. (C) Tumor volumes after different treatments. (D) Tumor weight of different groups after different treatment. (E) Body weight changes after different treatment during a period of time.