Redox and pH Dual-Responsive Polymeric Micelle with Aggregation-Induced Emission Feature for Cellular Imaging and Chemotherapy

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Statement of Purpose: Intelligent polymeric micelles for antitumor drug delivery and bioimaging have been the center of attentions due to the reduced systemic toxicity, enhanced antitumor efficacy and high efficiency in real-time imaging[1, 2]. However, the biological application of conventional fluorescence probes is limited by aggregation-caused quenching (ACQ) effect[3]. Thus, searching for aggregation-induced emission (AIE) fluorescence probes with high-efficiency, cost-effection and rapid visualization is in great need. Moreover, given the specific microenvironment of tumor has been widely utilized to engineer nanocarriers with stimuli responsive to enhance antitumor efficacy, the development of polymeric micelles feature with environment triggered drug release and great bioimaging ability is highly attractive.

Methods: The synthesis of mPEG-P (TPE-*co*-AEMA) was based on RAFT polymerization and amidation. The AIE active cellular imaging was evaluated by laser scanning confocal microscope (CLSM). DOX was encapsulated by a dialysis method and DOX-loaded micelles were injected to the tumor bearing mice via tail vein to evaluate the antitumor efficacy of DOX-loaded micelles and *in vivo* drug distribution.

Results: The particle size of DOX-loaded mPEG-P (TPE-*co*-AEMA) micelles was 68.2 nm with a narrow size distribution, which would be desirable for nanoparticles accumulating in tumor tissue via EPR effect. mPEG-P (TPE-*co*-AEMA) micelles did not show fluorescence in THF, but exhibited strong fluorescence in water due to the aggregation of TPE. The unique AIE feature and excellent biocompatibility of mPEG-P (TPE-*co*-AEMA) micelles made it suitable for cellular imaging. And intracellular drug release could be further monitored due to the AIE behavior of micelles. In addition, drug release from DOX-loaded micelles was triggered in a synergistical way of acid environment and high level of GSH, which was expected to enhance antitumor efficacy. Moreover, DOX-loaded micelles exhibited great antitumor efficacy *in vivo*, after a treatment cycle of 21 days, the tumor volume of DOX-loaded micelles group was around 370 mm^3, which was smaller than that of free DOX group (500 mm^3) and that of control group (1000 mm^3). Last but not the least, *EX vivo* fluorescent imaging demonstrated that these DOX-loaded micelles could efficiently accumulate in tumor site, which would further confirm the enhanced antitumor efficacy of DOX-loaded micelles.

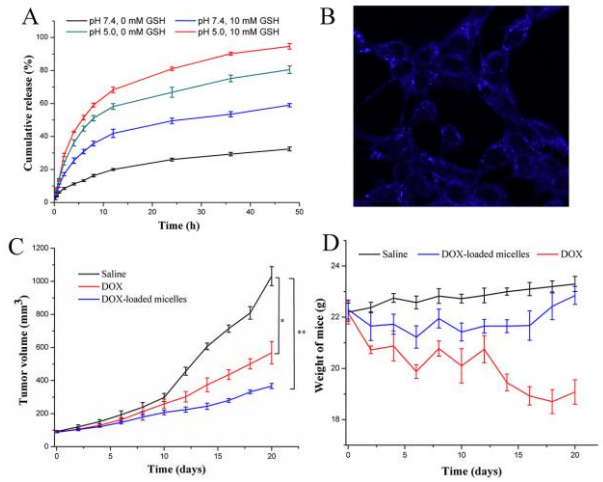

Figure 1. *In vitro* drug release of DOX-loaded mPEG-P (TPE-*co*-AEMA) micelles triggered with or without GSH (10 mM) at pH 7.4 and pH 6.5 (A); AIE active CLSM imaging under irradiation at 405 nm (B); Tumor volume of mice treated with saline, free DOX and DOX-loaded micelles (*$p < 0.05$, **$p < 0.01$ vs control group) (C); Body weight changes of mice after different treatments (D). Mice were injected with saline, DOX-loaded micelles and free DOX at day 0, 4, 8 and 12.

Conclusions: We have developed a multifunctional polymeric micelle with AIE labeled for environment triggered drug release and bioimaging. DOX-loaded micelles exhibited great antitumor efficacy *in vitro*, and the intracellular drug delivery could be monitored due to the unique AIE feature. Furthermore, DOX-loaded micelles exhibited better antitumor efficacy compared with free DOX with reduced side effects, and the DOX-loaded micelles could efficiently accumulate in tumor site. These results would provide new insights for designing high-efficiency visible nanocarriers for cancer diagnosis ad cancer therapy.

References:

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