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Based on poly (glutamic acid) conformation transition to control drug release and intracellular transport of nanoparticle for tumor targeting therapy

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The aim of this work was to connect the conformation of polypeptides with their bioactivity by preparing Dox-loaded nanoparticles using bioactive polymers with stimuli-responsive secondary structures and evaluating their anti-tumor activity. The bioactive polymer poly(L-glutamic acid)n-b-poly(D, L-lactic acid)m was synthesized and used to form doxorubicin-loaded hybrid polymeric nanoparticles to treat melanoma. These polymers exhibited pH responsive changes in conformation, which controlled the diverse functionalities of the nanoparticles. During circulation, poly(L-glutamic acid)n-b-poly(D, L-lactic acid)m protected Tat peptides on the nanoparticles from proteolysis. Under tumor-acidic conditions, polymers with shorter poly(L-glutamic acid) blocks underwent a conformational change to form channels that accelerated the release of doxorubicin[1]. The conformational change also exposed the Tat peptides to tumor cells, thereby promoting cellular internalization of the nanoparticles as shown in fig. 1.

Dox-loaded multifunctional nanoparticle based on bioactive polymers (PGAnb-PLAm) with pH-responsive conformation were constructed and characterized, and their anti-tumor activity was regulated by the conformational transition of PGAn-b-PLAm. PGAn-b-PLAm allowed the nanoparticle to protect Tatp against proteolysis and preserved it during circulation.

This approach provides a rational design for bioactive delivery systems that can keep vulnerable ligands (i.e., Tatp) intact during circulation and trigger their biological activity at pathological sites. Our work provides a strategy for applying bioactive polymers to the rational

construction of pH-responsive delivery systems for solid tumors and lends insight into possible conformational effects on the bioactivity of drug carriers.

Keywords: Control drug release; Intracellular transport; Nanoparticle; Tumor targeting therapy

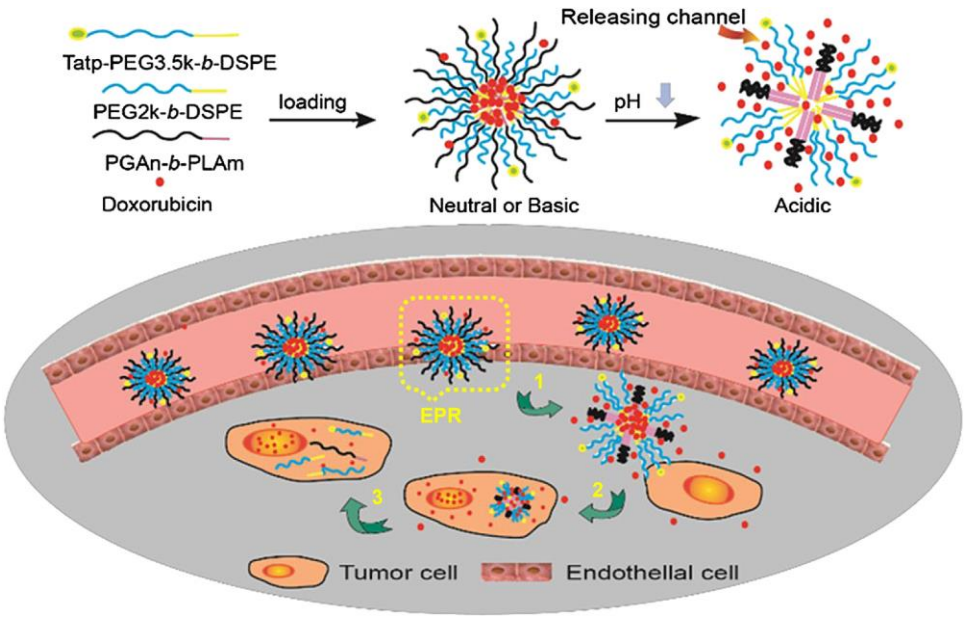

Fig.1. Illustration of poly (L-glutamic acid)-based hybrid nanoparticles for intracellular delivery of doxorubicin (Dox). The accumulation of the nanoparticles tumor tissues are partially based on the EPR effect (1). Under tumor-acidic conditions, PGAn-b-PLAm undergoes a conformational change to expose Tat peptides to tumor cells, which promotes cellular uptake of the micelles (2). The conformational change also produces channels that accelerate the release rate of Dox (3).

Reference

[1] Wang Q M, Gao Z G, Liu S, et al. Hybrid polymeric micelles based on bioactive polypeptides as pH-responsive delivery systems against melanoma. Biomaterials. 2014, 35(25): 7008-7021.