Sequential and Site-Specific Delivery of Dual Anticancer Therapeutics Using Programmed Nanodepots

Tianyue Jiang,[†] Ran Mo,[†] Adriano Bellotti, Jianping Zhou, Zhen Gu*
Joint Department of Biomedical Engineering, North Carolina State University and University of North Carolina at Chapel Hill, NC 27695, USA; Molecular Pharmaceutics Division, Eshelman School of Pharmacy, Chapel Hill, NC 27599, USA.

Statement of Purpose: Combination therapy holds great promise in enhancing antitumor activity by achieving synergistic effects and reducing toxicity.[1-3] The distinct pharmacokinetic profiles and subcellular targeting sites of various therapeutic drugs are chief obstacles of combination therapeutic effect. To address this dilemma, the nanoparticle-based drug co-delivery systems have been developed to unify their individual pharmacokinetic behavior of different guests, such as such as polymeric nanoparticles,[4-6] liposomes,[7] nanocomplex[8-10] and inorganic nanoparticles.[11] Such individual nanocarrier encapsulating multiple anticancer agents, including small drugs, siRNA, plasmid DNA or protein/peptide shuttles different drugs toward the same destination via the enhanced permeability and retention (EPR) effect and active targeting effect. However, for drugs with distinct targeting sites, either in the tumor environment or subcellular positions, these co-delivery nanosystems lacking of site-specific delivery function can hardly achieve the maximum therapeutic efficacy. Delivering combination drugs to their specific targeting sites in a sequentially controlled release fashion still remains challenging.

Methods: We fabricated gel-liposome (Gelipo) with a liposomal core and a crosslinked HA shell for sequential and site-specific delivery of TRAIL and Dox (Figure 1)[12].

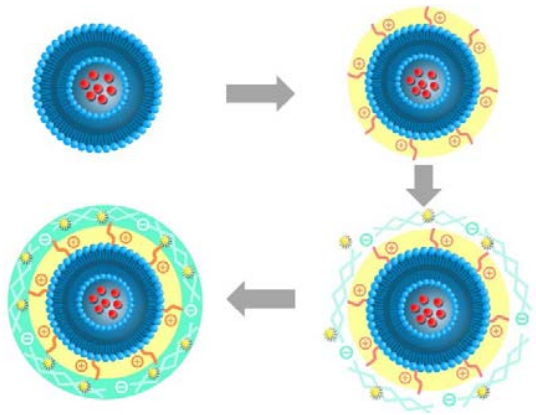

Figure 1. Schematic design of the preparation of TRAIL/Dox-Gelipo.

Results: The particle size and zeta potential of Gelipo is about 120nm, 25mV, respectively. The degradation of the HA shell by HAase that is concentrated in the tumor environment resulted in the rapid extracellular release of TRAIL and subsequent internalization of the liposomes. The parallel activity of TRAIL targeting the cell membrane and Dox targeting the nucleus showed synergistic anticancer efficacy. The half-maximal inhibitory concentration (IC50) of TRAIL and Dox co-loaded Gelipo (TRAIL/Dox-Gelipo) toward the human breast cancer (MDA-MB-231) cells was 86 ng/mL (Dox concentration), a 5.3-fold increase compared to that of Dox-loaded liposomes (Dox-R8H3-L). Moreover, Gelipo with a programmed choreography displayed a remarkable tumor accumulation and significantly improving the inhibition of the tumor growth in the MDA-MB-231 xenograft tumor animal model.

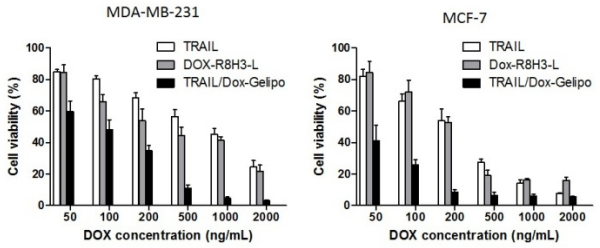

Figure 2. In vitro cytotoxicity of TRAIL, Dox-R8H3-L and TRAIL/Gelipo on MDA-MB-231and MCF-7 cells for 24 h.

Conclusions: Gelipo based design for sequential and site-specific delivery of TRAIL and Dox will open an avenue for the exploration of more sophisticated drug derlivery systems, which can synergistically differentiate the extracellular and intracellular target to promote a superior anticancer effect.

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