Scalable and Cleavable Polysaccharide Nano-Carriers for Multifunctional Theranostics

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While polysaccharide-based nano-carriers have been recognized for their crucial roles in tumor theranostics, the industrial-scale production of nanotherapeutics still remains a significant challenge. Most current approaches adopt a postpolymerization self-assembly strategy that follows a separate synthetic step and thus suffers from subgram scale yields and a limited range of application. To address this challenging, herein we demonstrate the kilogram-scale formation of polysaccharide–polyacrylate nano-carriers at concentrations of up to 5 wt% through a one-pot approach – starting from various acrylate monomers and polysaccharides – that combines aspects of hydrophobicity-induced self-assembly with the free radical graft copolymerization of acrylate monomers from polysaccharide backbones into a single process that is thus denoted as a Graft copolymerization Induced Self-Assembly (GISA). We also demonstrate that this novel approach is applicable to a broad range of polysaccharides and acrylates. Notably, by choosing a crosslinker that bears a disulfide group and two vinyl capping groups to structurally lock the nano-carriers, the products are rendered cleavable in the reducing environments encountered at tumor sites and thus provide ideal candidates for the construction of anticancer nanotherapeutic systems. *In vitro* and *in vivo* studies demonstrated that the use of this nano-carrier for the delivery of doxorubicin hydrochloride (DOX) significantly decreased the side effects of DOX and improved the bio-safety of the chemotherapy accordingly.

Drug resistance is one of the important factors resulting into tumor metastasis, gene therapy combined with chemotherapy has become an effective way to induce the apoptosis of drug-resistant tumor cells. On this basis, the cleavable polysaccharide nano-carriers were used to co-deliver the negatively charged siRNA and hydrophobic/hydrophilic chemotherapeutics, such as carboplatin and paclitaxel. The resultant multi-drug loaded nano-carriers displayed great potential in fighting drug-resistant tumor cells. On this basis, we envision that these nano-carriers will contribute to the development of tumor nanotheranostics that combine the biological functionalities of polysaccharides with the unmatched application-specific flexibility of nano-carriers.

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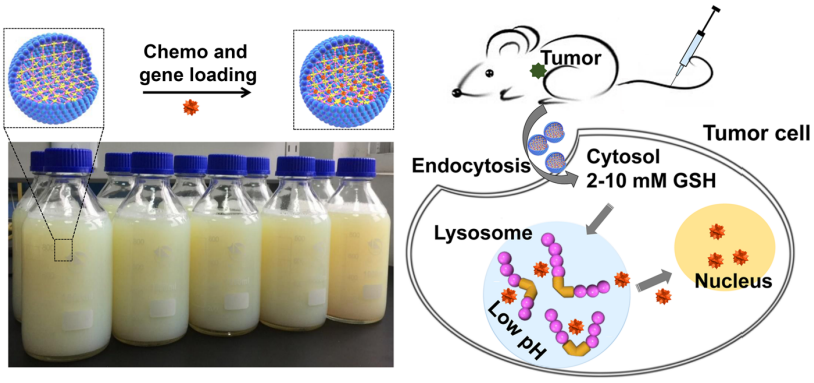


Figure 1. Schematic illustration depicting the fabrication and tumor environment-induced cleavage of the scalable polysaccharide nano-carriers.

References

1. Wang, H; Dai, T.; Li, S.; and Dou, H. et al. Acta Biomaterialia, 2018, 72, 206-216.
2. Wang, H; Dai, T.; Lu, Bo.; and Dou, H. et al. Chinese J. Polym. Sci., 2018, 36, 391-398.
3. Wang, H.; Dai, T.; Zhou, S.; and Dou, H. et al. Scientific Reports, 2017, 7, 40011.
4. Dai, T.; Zhou, S.; Dou, H.; Cao, Y.; and Zhou, G. et al. Biomaterials, 2014, 35, 8227-8235.
5. Zhou, S.; Min, X.; Dou, H. et al. Chem. Commun., 2013,49, 9473-9475.
6. Zhou, S.; and Dou, H. et al. Polymer Chemistry, 2013, 4, 4103-4112.

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