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Prodrug Systems (I): Lipid-Based Doxorubicin Prodrugs and Their Nanodelivery Systems

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Abstract Using natural lipids to covalently connect with antitumor agents to construct lipid-based molecular prodrugs and their nanosystems is a promising research frontier for sustainable medicinal chemistry, nanobiotechnology and tumor chemotherapy. This paper reviewed recent progress of lipid-based doxorubicin (molecular) prodrugs and their nanodelivery systems, including lipid-doxorubicin prodrugs, stimuli-responsive lipid-doxorubicin prodrugs, and lipid-doxorubicin prodrug-based drug co-delivery nanosystems. Additionally, possible future research outlooks in this field were also discussed.

Keywords lipid, doxorubicin, prodrugs, stimuli-responsive, drug co-delivery, nanosystems

Transformation of renewable and biocompatible natural lipid resources into new functional biomaterials[1] has been highly focused for nurturing sustainable development. Natural lipids (especially aliphatic lipids, steroid lipids, and fat-soluble vitamins) play vital roles, including in membrane formation, hormone metabolism and cell signal transduction in living organisms. Their controllable physicochemical properties, high biocompatibility and special biological functions make them good sustainable building blocks for the construction of nanostructured biomaterials and delivery systems.[2]

As a promising research area, some natural lipids have been used to covalently connect chemotherapeutic agents to prepare natural lipid-based molecular prodrugs recently.[3] Compared to the (lipid) polymeric prodrug counterparts,[4] lipid-based molecular prodrugs were able to improve drug loading efficiency, enhance cellular uptake, facilitate drug delivery in the subcellular system, increase bioavailability, and so on. Through nano-engineering, lipid-based molecular prodrugs/conjugates can be self-assembled into controllable nano-aggregates with other amphiphilic lipids (or helper lipids), making them efficient building blocks for nano-formulations towards cancer treatment.[5] Lipid-based molecular prodrugs of doxorubicin (DOX), a model antitumor agent, have attracted increasing attention in recent years.[6] To further enhance chemotherapeutic efficacy, developing stimuli-responsive and programmable doxorubicin prodrug delivery systems that respond to different intracellular biochemical triggers (*e.g.*, pH, redox, enzyme, *etc*.) could effectively reduce drug-resistance, elevate bioavailability, improve site-specific transport, and facilitate controlled release. Some systems, including pH-sensitive oleic acid-DOX prodrug/ApoB-100,[7] pH-sensitive NE-C16-DOX nanoemulsion,[8] pH-sensitive and tumor targeting TPGS-CH=*N*-DOX/DSPE-PEG-cRGD prodrug nanomicelles,[9] bioreduction-responsive prodrug mPEG-CD/Ada-SS-doxorubicin[10], as well as phospholipase D (PLD) enzyme-responsive phosphatidyl-DOX prodrug,[11] were developed. However, the therapeutic efficiency of single-component prodrug is greatly limited by several factors such as disease complexity, multidrug resistance (MDR) and off-targeting effect.[12] To address the limitations of single-component doxorubicin prodrug systems, some lipid-based doxorubicin prodrug co-delivery systems have been reported.[13] Ni *et al*. co-delivered DOX-gemcitabine prodrug and vincristine by lipid carrier to treat lymph cancer.[14] Kuai *et al*. developed pH-sensitive sHDL-DOX prodrug-loaded high density lipoprotein (HDL)-mimicking nanodiscs for combination chemoimmunotherapy.[15] These works indicated that lipid doxorubicin (molecular) prodrug-based nanomaterials can be employed as potential drug co-delivery systems. Apart from the drug-drug co-delivery system, developing “nano-cocktails” to co-deliver doxorubicin/genes is also an efficient approach to overcome MDR and inhibit the anti-apoptotic process,[16] thus achieving a synergistic therapeutic effect. Notably, the natural lipid-based doxorubicin prodrug/gene co-delivery systems with the merits of low cost, high biocompatibility, smart and programmable delivery properties are still rare. The construction of lipid-based doxorubicin prodrugs and their nanodelivery systems is illustrated in Figure 1.

Regarding the future of natural lipid-based doxorubicin prodrugs nanodelivery systems, there are still vast spaces for extensive research and development, including: (1) exploring green, efficient, controllable and modular methods/strategies to synthesize natural lipid-based doxorubicin prodrugs and prepare their nanoassemblies; (2) expanding the structure/function diversity of the natural lipid-based doxorubicin prodrugs, especially “smart” (stimuli-responsive, multifunction-integrated, receptor targeting, bio-recognition, *etc*.) natural lipid-based doxorubicin prodrugs towards precision and personalized medicine; (3) elucidating the structure-function relationship (SFR) between the structures of natural lipid-based doxorubicin prodrugs and their physicochemical/biological functions; (4) based on *in vitro* bioevaluation data, optimizing the natural lipid-based doxorubicin prodrugs and their nanodelivery systems to realize programmable and synergistic

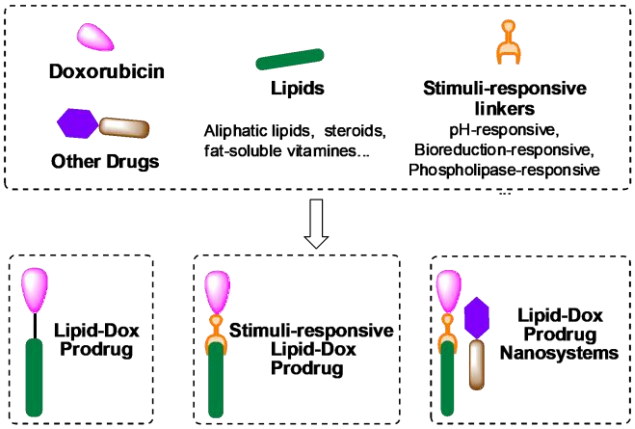

Figure 1 Construction of lipid-based doxorubicin prodrugs and their nanodelivery systems.

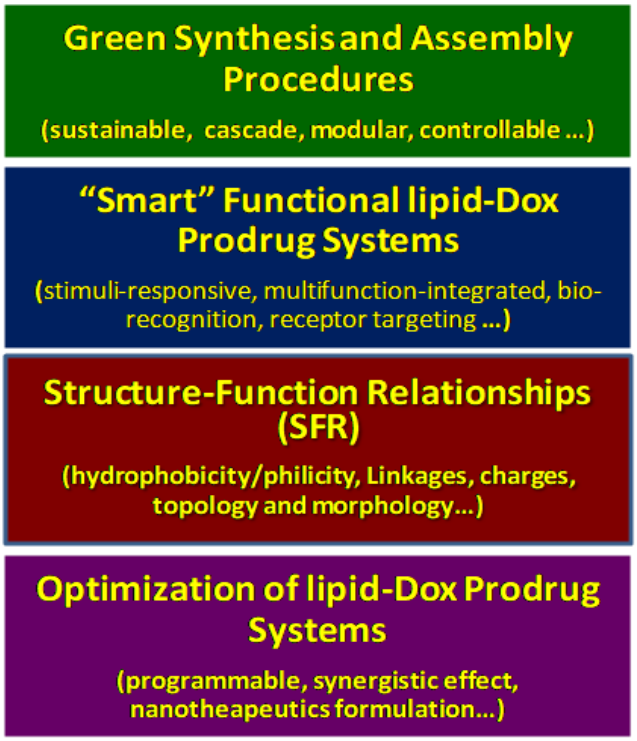

Figure 2 Future perspective of lipid-based doxorubicin prodrugs and their nanodelivery systems.

therapeutic drug/gene co-delivery towards high-performance combo-chemo-gene-therapy.[17] The above-mentioned areas are needed to be systematically addressed (Figure 2).

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Conflict of Interest

The authors declare no conflict of interest.

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