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Prodrug Systems (II): A Perspective of Polymer-Based Doxorubicin Prodrug Systems towards Chemotherapy

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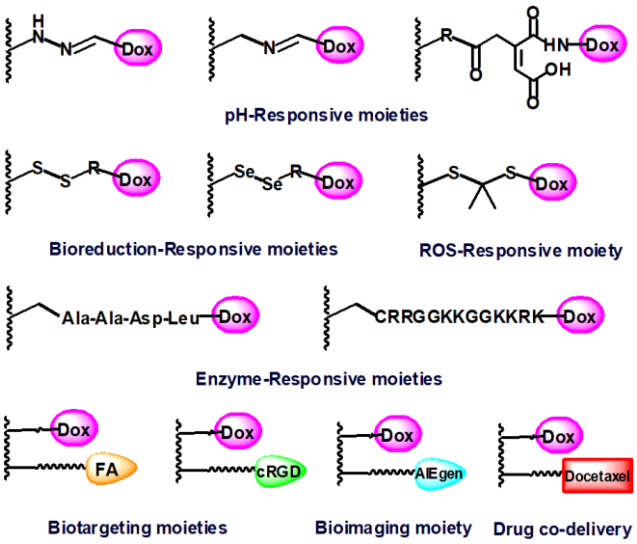
Abstract Utilizing biocompatible polymers as platforms to covalently conjugate with chemotherapeutics to construct polymer-based prodrugs and their nano drug delivery systems has attracted great attention in recent years. This perspective reviewed state-of-the-arts for polymer-based doxorubicin prodrugs and the related nanodelivery systems, including: (1) pH-responsive polymer-doxorubicin prodrugs/conjugates; (2) pH/redox-dual responsive prodrugs/conjugates; (3) reactive oxygen species/hypoxia-responsive polymer-doxorubicin prodrugs; (4) tumor receptor targeting polymer prodrugs; (5) enzyme-responsive polymer-doxorubicin prodrugs. Finally, possible future perspectives were also stated and discussed.

Keywords polymers, doxorubicin, prodrug, stimuli-responsive, drug delivery, nanosystem

Developing prodrugs as chemotherapeutic agents is a rapid growing and promising research field. Efficient prodrugs or conjugates need to meet the requirements of low serum protein binding, high stability in blood circulation, reticuloendothelial system (RES)-mediated immune clearance, tumor accumulation and high cellular internalization.[1] To achieve high drug delivery efficiency, it is essential to design prodrugs or conjugates with good water solubility, controllable structures and molecular weight, tunable nanoaggregate architecture, as well as enhanced drug loading/encapsulation capacity.[1,2]

In general, prodrug-based chemotherapeutic system could be divided into two categories: small molecular prodrugs and polymer-based prodrugs. Compared to small molecular prodrug counterparts,[3] polymer-based prodrugs exhibit higher stability, prolonged blood circulation time, higher drug loading efficiency, enhanced cellular uptake, increased bioavailability, and so on. Most studied polymer-based prodrugs are polymer-doxorubicin (Dox) conjugates. Some tumor-related factors, such as low pH, bioreductive substances GSH, reactive oxygen species (ROS), as well as specific protease, could be used to trigger prodrug release through specific biochemical reactions and then improve the chemotherapeutic performance. Accordingly, smart and stimuli-responsive polymer-doxorubicin prodrugs were developed as these following types: (1) pH-responsive polymer-oxorubicin conjugates, such as: acid-labile *cis*-aconityl containing mPEG-*b*-PAE-*cis*-DOX prodrug,[4] SPAAC-click-onjugates mPEG-*b*-PLA-*g*-DOX,[5] pH-induced charge conversion prodrug PLL (CB/DOX)-*b*-PMPC,[6] cyclodextrin-ased supramolecular prodrug PRMO@DOX,[7] pluronic pH-sensitive prodrug P123-CAD/F127-PBA,[8] with these prodrugs normally containing pH-sensitive (4.5—6.5) linkage bonds including Schiff-base, hydrozone and aconityl; (2) pH/redox-dual responsive prodrugs/conjugates, such as: hyper-branched polyglycerol (hPG)-based NG-DOX conjugates,[9] EG2K-SS-CBA-DOX prodrug,[10] pH/GSH-sensitive prodrug PDPAO@imine-DOX/*cis*-6MP,[11] cross-linked dendritic MPEG-*b*-PAMAM-LA/DOX prodrug[12] and pH/bioreduction-dual responsive [PEEP-*b*-(PBYP-*hyd*-DOX)-Se]$_2$ prodrug,[13] these prodrugs having pH-sensitive moieties and redox-sensitive moieties (disulfide/diselenide linkages) in certain positions; (3) reactive oxygen species (ROS)/hypoxia-responsive polymer-doxorubicin prodrugs, such as ROS/PDT-dual functional prodrug nanosystems PEG-TK-DOX@pheophorbide A (PhA)[14] and Ce6@PPE-TK-DOX,[15] in which thioketal acts as the ROS-cleavable linker; (4) tumor receptor targeting polymer-doxorubicin prodrugs, such as: FA-P(MPC-*co*-PEGMA-BZ)-*g*-DOX prodrug (targeting: Folate receptor)[16] and TPGS-CH=*N*-DOX/DSPE-PEG-cRGD (targeting: intergrin),[17] whose biotargeting effect greatly depends on the density of targeting moieties (optimum: 5%—10% molar ratio); and (5) enzyme-responsive polymer-doxorubicin prodrugs, such as pH/legumain enzyme-dual responsive prodrug-carbon dot CDs-C9-AANL-DOX.[18] The related study is relatively rare due to the synthesis bottleneck of enzyme-cleavable peptide linkers. Besides, there are some multi-stimuli (photo/redox-dual responsive,[19] pH/GSH/cathepsin B-triple responsive[20] and pH/redox/AIEgen prodrug theranostic[21]) systems that have been newly developed. These promising works showed that the smart and stimuli-responsive polymer-doxorubicin prodrugs could be employed as potential chemotherapeutic systems. However, the therapeutic efficiency of single-component prodrug is greatly limited due to several factors such as disease complexity, multidrug resistance (MDR) and off-targeting effect.[22] To overcome these disadvantages, polymer-doxorubicin-based co-delivery system such as CAD-PLGA-PEG-PLGA-CAD-doxorubicin/docetaxel for *in situ* synergistic chemotherapy,[23] has been developed. Compared to multidrug co-delivery systems, only few biocompatible polymer-based doxorubicin/gene co-delivery (*e.g.*, dox-P53DNA *co*-delivery mPEG-*b*-PBYP-*hyd*-DOX/mPEG-*b*-PBYP-*g*-DAE nanocarrier)[24]

Scheme 1 Various types of polymer-based doxorubicin conjugates/prodrug systems



systems have been developed. Up to date, creating a doxorubicin/gene programmable co-delivery system to achieve synergistic effect, overcome MDR and inhibit the anti-apoptotic process is still a not-fully developed area. The polymer-based doxorubicin prodrugs are shown in Scheme 1.

For the future outlook of polymer-based doxorubicin prodrug chemotherapeutic systems, we can expect the research and development (R & D) in the following areas: (1) using natural-based sustainable resources,[25] such as: polysaccharides, polypeptides/peptoids and polylipids/lipoids, along with green, efficient, controllable and modular methods/ strategies to synthesize natural polymer-based doxorubicin prodrugs/conjugates; (2) expanding the structure/function diversity of the polymer-based doxorubicin prodrugs, especially "smart" (stimuli-responsive, multifunction-integrated, receptor targeting, bio-recognition, *etc*.) polymer-based doxorubicin prodrugs towards precision and personalized medicine; especially, it is worth integrating polymer-doxorubicin prodrugs with ^{18}F, ^{64}Cu-based positron electron tomography (PET) system or functional inorganic nanoparticles[26] for creating efficient multi-channel prodrug-based theranostics; (3) Elucidating the structure-function relationship (SFR) between the architectures of polymer-based doxorubicin prodrugs/ conjugates and their physicochemical/biological functions; (4) Based on *in vitro* bioevaluation data, optimizing the (natural) polymer-based doxorubicin prodrugs and their nanodelivery systems for programmable/synergistic theranostic performance; (5) Artificial intelligence assisted design (AIAS) and simulation of polymer-based prodrug system towards post-information biomedicine era. It is necessary to rationally and systematically address the above-mentioned topics (Scheme 2).

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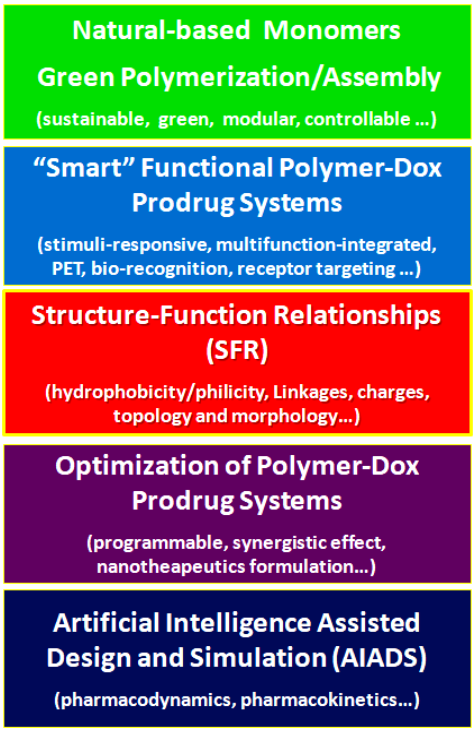
Scheme 2 Future perspective of polymer-based doxorubicin prodrugs and their nanodelivery systems



Conflict of Interest

The authors declare no conflict of interest.

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