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Stimuli-responsive cross-linked micelles for on-demand drug delivery against cancers ☆

Yuanpei Li [a,*,1], Kai Xiao [a,1], Wei Zhu [b], Wenbin Deng [a], Kit S. Lam [a,**]

[a] Department of Biochemistry & Molecular Medicine, UC Davis Cancer Center, University of California Davis, Sacramento, CA 95817, USA
[b] Department of Cardiology, the First Affiliated Hospital of Zhejiang University, School of Medicine, Zhejiang University, Hangzhou 310003, China

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ABSTRACT

Stimuli-responsive cross-linked micelles (SCMs) represent an ideal nanocarrier system for drug delivery against cancers. SCMs exhibit superior structural stability compared to their non-cross-linked counterpart. Therefore, these nanocarriers are able to minimize the premature drug release during blood circulation. The introduction of environmentally sensitive cross-linkers or assembly units makes SCMs responsive to single or multiple stimuli present in tumor local microenvironment or exogenously applied stimuli. In these instances, the payload drug is released almost exclusively in cancerous tissue or cancer cells upon accumulation via enhanced permeability and retention effect or receptor mediated endocytosis. In this review, we highlight recent advances in the development of SCMs for cancer therapy. We also introduce the latest biophysical techniques, such as electron paramagnetic resonance (EPR) spectroscopy and fluorescence resonance energy transfer (FRET), for the characterization of the interactions between SCMs and blood proteins.

Contents

1. Introduction

Nanotechnology offers new opportunities for diagnosis and treatment of a variety of cancers [1–5]. Multifunctional nanoparticles possessing functions including tumor targeting [6–10], imaging [11–14] and therapy [10,15–17] are under intensive investigation aiming to overcome limitations associated with conventional cancer diagnosis and therapy [18–20]. Over the past decade, polymeric micelles

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* Correspondence to: Y. Li, Department of Biochemistry & Molecular Medicine, UC Davis Cancer Center, University of California Davis, Sacramento, CA 95817, USA. Tel.: +1 916 734 0905; fax: +1 916 734 6415.
** Correspondence to: K. S. Lam, Department of Biochemistry & Molecular Medicine, UC Davis Cancer Center, University of California Davis, Sacramento, CA 95817, USA. Tel.: +1 916 734 0910; fax: +1 916 734 7946.
E-mail addresses: liyuanpei@gmail.com (Y. Li), kit.lam@ucdmc.ucdavis.edu (K.S. Lam).

[1] Yuanpei and Kai contributed equally to this work.

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have been extensively investigated as nanocarriers to deliver conventional anticancer drugs. These nanoparticles provide several distinct advantages for the drugs, such as improved solubility, prolonged *in vivo* circulation time and preferential accumulation at tumor site via the enhanced permeability and retention effect [21–24]. Despite the recent progress in the research of micellar nanoparticles, some shortcomings are gradually revealed which may limit their application in clinic. In blood circulation, blood proteins and lipoproteins such as high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and chylomicron may interact with the polymeric micellar nanoparticles [25]. This process can result in the early disintegration or aggregation of micelles and premature drug release [26]. Besides, polymeric micelles are thermo-dynamic self-assemble system which has a well-known equilibrium existed between micelles and unimers (assembly unit) in aqueous condition. After being injected into the blood stream, conventional self-assembled polymeric micelles are susceptible to dilution below the critical micelle concentration (CMC). This may lead to the dissociation of micelles into unimers.

Cross-linking strategy has been utilized to solve the above mentioned stability problems following the pioneer work by Wooley's group [27]. Since then, this strategy has been exploitedby a number of other groups [28–33]. Covalent cross-links between specific domains of the micelles are formed in order to improve the micelles' structural stability suitable to drug delivery rather than the weak non-covalent intermolecular hydrophobic interactions existing in the conventional polymeric micelles that facilitate polymer micelles assembly and integrity [27]. To be more effective, anticancer drugs should be released exclusively in tumor tissue or inside tumor cell. However, excessively stabilized micelles may prevent the drug from releasing to target sites, thus reducing the therapeutic efficacy [28,29]. Stimuli-responsive cross-linked micelles (SCMs) are introduced to improve the drug delivery [30–33]. SCMs exhibit unique stability in blood circulation and can better retain the drug contents. The utilization of environmentally sensitive cross-linkers or assembling units makes SCMs responsive to single or multiple stimuli in the microenviroment of tumor site or inside the tumor cells [34,35] or the application of exogenous stimuli (Fig. 1). The cleavage of the intra-micellar cross-linkage or disassembly of the micelles responding to stimuli leads to exclusively drug release in the target site [36,37]. The special micelles are often called 'smart' or 'intelligent' micellar nanoparticles. This review briefly summarizes the recent advances in stimuli-responsive cross-linked micellar nanocarriers with the main focus on the design, characterization, cross-link strategy, protein interaction, stimuli-sensitive release mechanism and preclinical evaluation.

2. Main text

2.1. Design of stable SCMs with single or multiple responsive properties

The basic elements need to be considered in the design of SCMs include how and where to introduce cross-linkages to the micelles and how to endow the micelles with responsiveness to the microenvironments of the target sites or exogenous stimuli. The cross-linkage can be introduced at the hydrophilic shell [38,39], hydrophobic core [26,40,41] or core–shell interface [35,42] of the micelle via chemical cross-link, photo cross-link or polymerization after the micelle formation via self-assembly in aqueous solution. Recently, *in situ* cross-linking approach has been reported by several groups. In this case, one or two types of cross-linkable pendants are introduced to the assembly units so that the micelles can be cross-linked spontaneously during the micelle formation [43,44]. The reported stimuli for drug delivery include pH, temperature, enzymes, electrolytes, redox (reduction/oxidization), ultrasound, light and magnetic field [45–47]. Very recently, a few studies have been succeeding in systemically applying exogenous stimuli via FDA approved agents, such as N-Acetylcysteine (a reducing agent) and mannitol (a cis-diol) [43,44]. The responsiveness of SCMs refers to

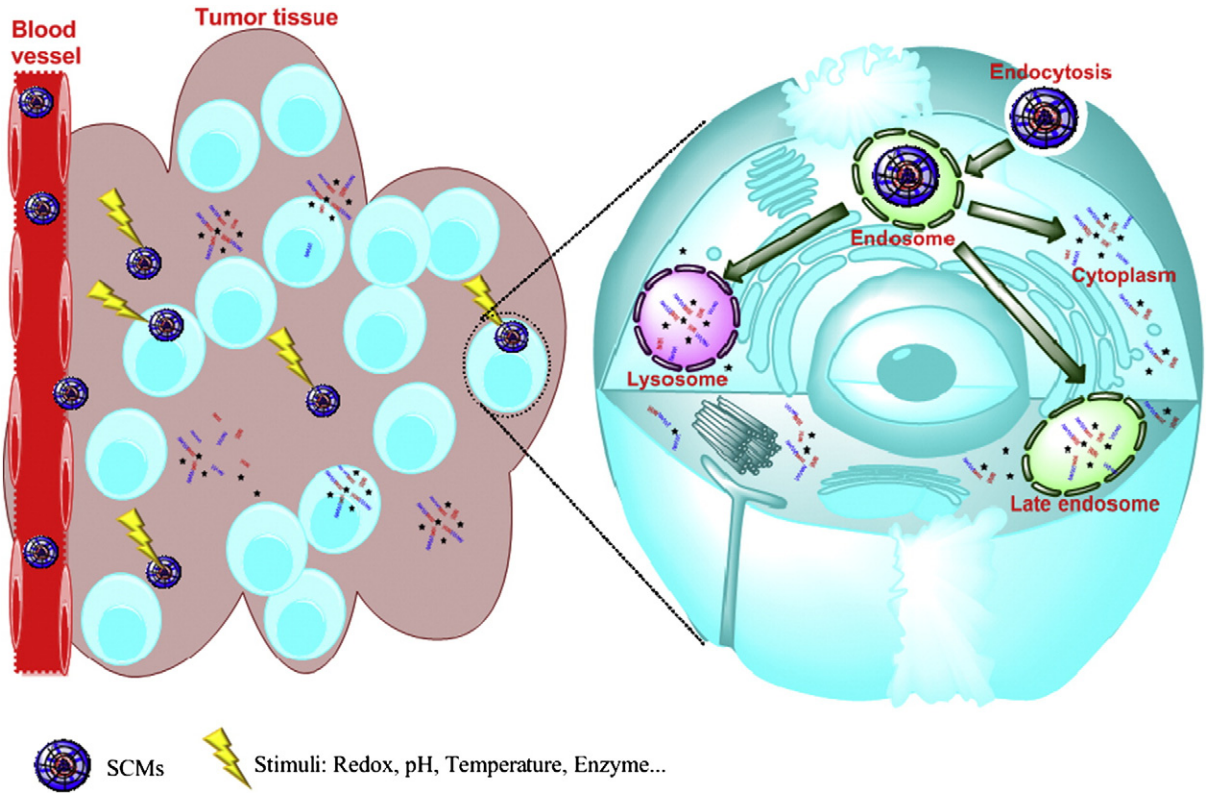

Fig. 1. Schematic illustration of stimuli-responsive cross-linked micelles (SCMs) for cancer therapy.