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Mini Review

Charge Switchable Polymer Micelles: A Smart Strategy for Safe and Efficient Drug Delivery in Cancer Therapy

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Abstract

The development of safe and targeted drug delivery by the polymer micelles is still impeded by the side effect, undesired drug release, and inefficient cell uptake of the anti-cancer drug. This article discussed the design and features of the charge switchable polymer micelles for safe and efficient drug delivery in cancer therapy.

Keywords: Charge switchable; Polymer micelle; Drug delivery; Stimuli-response; Anti-cancer

Abbreviations: PMs:Polymer Micelles; DDS:Drug Delivery Systems; EPR: Enhanced Permeation and Retention

Mini review

Cancer, one of the deadliest disease on worldwide scale, has caused serious impact to the human health, which has gained tremendous interests of scientists from laboratory research to clinic [1]. Over the past few decades, the polymer micelles (PMs) have been widely utilized in the efficient delivery of anti-cancer drugs, that is, drug delivery systems (DDS) [2]. Commonly, the conventional PMs used in DDS can accumulate at the tumor site by the passive targeting mechanism such as the enhanced permeation and retention (EPR) effect resulting from the specific size of the polymer micelles. Unfortunately, although hundreds of PMs-based anti-cancer drugs have been developed, only few of them have been applied in clinic. In brief, the side effect of the encapsulated anti-cancer drug in blood circulation the PMs and inefficient uptake in the tumor cell are the bottlenecks for development of PMs based DDS in cancer therapy. For actual application in clinic, the PMs based DDS should possess long half-life time in blood circulation, high cellular uptake at the tumor site, and efficiently intracellular drug release. Nevertheless, for conventional PMs based DDS, disassembly of the PMs and interactions with serum protein usually occurs after intravenous injection in blood circulation, which will cause serious toxicity and side effect to human body. Secondly, when approaching to the tumor, conventional PMs cannot efficiently accumulate at the tumor site causing rather low cellular uptake of the anti-cancer drugs. Therefore, design of a smart PMs based DDS that can achieve both prolonged half-life time in blood circulation and high cellular uptake is of great importance for application of PMs in anti-cancer drug delivery. To balance the obstacle between the safety in blood circulation and high cellular uptake at tumor site, the surface charge of the PMs is expected to be changeable under different physiological conditions, that is, the charge switchable PMs [3]. For instance, negatively charged PMs cause less interactions with serum protein and cell membrane, which can improve *in vivo* biosafety with long half-life time in blood circulation. On the other hand, the positively charged PMs show good affinity to negatively charged cell membranes at the tumor site. Therefore, due to the differences between normal physiologic condition (pH 7.2~7.4) and tumor extracellular pH (pH 6.5~6.9), pH sensitive PMs are widely used as the charge switchable vehicle for efficient anti-drug delivery. Moreover, another feature of the charge switchable PMs is the so-called "proton sponge effect" [4]. When uptake by the cancer cell, the anti-cancer drugs encapsulated in the PMs need to escape from the endosomes and release into the cytoplasm, thus, the proton sponge effect can increase the ionic concentration inside the endosome membrane causing a swelling structure by osmotic pressure, and finally breaking down of the

membrane. Because of the pH buffer capacity of the polymer chain, charge switchable PMs with endosomolytic property can escape the endosome, which can be used to achieve efficient drug release via the proton sponge effect. In brief, the charge switchable PMs by pH sensitivity are the promising drug vehicle with prolonged blood circulation, high tumor accumulation, and efficient intracellular drug release for cancer therapy.

Recently, several kinds of charge switchable PMs have been developed, which have shown both improved biosafety and high tumor accumulation in cancer therapy, such as PCL-b-PEI/amide-FA by Shen's group [5], poly(L-glutamic acid-co-L-lysine) by Chen's group [6], and RGD-conjugated polypeptide by Chen's group [7]. Liu's group developed the charge switchable PEG-b-PLL block copolymer micelles for drug co-delivery to enhance cellular uptake and reverse the multidrug resistance effect [8] (Figure 1). Shen's group developed charge-reversal poly{N-[2-(acryloyloxy)ethyl]-N-[p-acetyloxyphenyl]-N,N-diethylammonium chloride} as gene-delivery carrier for cancer treatment [9]. Moreover, a novel PLL(CB/DOX)-b-PMPC that exhibited the pH-triggered charge-conversion property was prepared and applied as potential nanocarriers for cancer therapy [10]. Recently, our group has developed the poly (lysine-co-N,N-bis(acryloyl) cystamine-codimethylmaleic anhydride) with stepwise pH-responsible charge switchable property, which can achieve reversion of the surface charge from negative to positive in response to different physiological conditions [11]. Additionally, to avoid the premature drug release of the PMs our group designed a crosslinked polypeptide micelle with switchable surface charge and endosome escape property by proton sponge effect for efficient drug intracellular delivery [12].

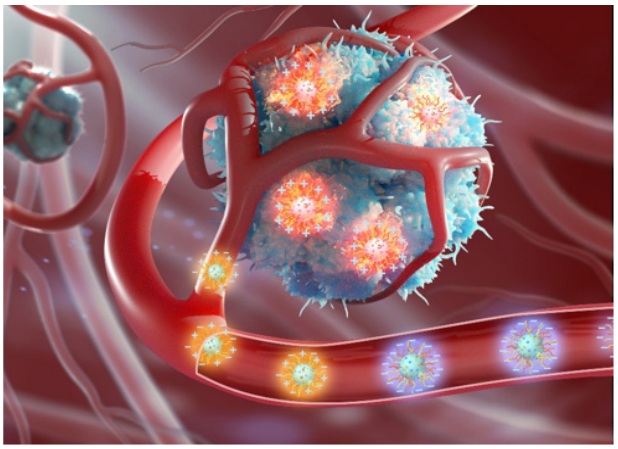

Figure 1: The stepwise charge switchable polymer micelles for tumor accumulation [9].

Conclusion

In summary, although the as described charge switchable PMs possess many features such as prolonged half-life time in blood circulation, high accumulation at tumor site, and endosome escape for intracellular drug delivery, some shortcomings still need to be overcome, for example, complicated synthesis route, degradation of the PMs after drug release, and high cost for clinical use. Therefore, the novel PMs based DDS that can solve the above-mentioned problems are still needed in the future work.

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References

1. Chadha AS, Khoo A, Aliru ML, Arora HK, Gunther JR, et al. (2016) Recent advances and prospects for multimodality therapy in pancreatic cancer. Semin Radiat Oncol 26(4): 320-337.
2. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE (2001) Biodegradable polymeric nanoparticles as drug delivery devices. J Controlled Release 70(1-2): 1-20.
3. Wang Y, Lv S, Deng M, Tang Z, Chen X (2016) A charge-conversional intracellular-activated polymeric prodrug for tumor therapy. Polym Chem 7(12): 2253-2263.
4. Ke Z, Yang L, Wu H, Li Z, Jia X, et al. (2018) Evaluation of *in vitro* and *in vivo* antitumor effects of gambogic acid-loaded layer-by-layer self-assembled micelles. Int J Pharm 545(1-2): 306-317.
5. Xu PS, Van Kirk EA, Zhan Y, Murdoch WJ, Radosz M, et al. (2010) Targeted charge-reversal nanoparticles for nuclear drug delivery. Angew Chemie Int Ed English 46(26): 4999-5002.
6. Huang Y, Tang Z, Zhang X, Yu H, Sun H, et al. (2013) pH-Triggered charge reversal polypeptide nanoparticles for cisplatin delivery: preparation and *in vitro* evaluation. Biomacromolecules 14(6): 2023-2032.
7. Lin WF, Ma GL, Yuan ZF, Qian HF, Xu LB, et al. (2019) Development of zwitterionic polypeptide nano-formulation through charge attraction assembly for targeted drug delivery. Langmuir 35(5): 1273-1283.
8. Huo Q, Zhu JH, Niu YM, Shi HH, Gong YX, et al. (2017) pH-triggered surface charge-switchable polymer micelles for the co-delivery of paclitaxel/disulfiram and overcoming multidrug resistance in cancer. Int J Nanomedicine 12: 8631-8647.
9. Qiu NS, Gao JQ, Liu Q, Wang JQ, Shen YQ (2018) Enzyme-responsive charge-reversal polymer-mediated effective gene therapy for intraperitoneal tumors. Biomacromolecules 19(6): 2308-2319.
10. Ma BX, Zhuang WH, Wang YA, Luo RF, Wang YB (2018) pH-sensitive doxorubicin-conjugated prodrug micelles with charge-conversion for cancer therapy. Acta Biomater 70: 186-196.
11. Qu J, Peng S, Wang R, Yang ST, Zhou QH, et al. (2019) Stepwise pH-sensitive and biodegradable polypeptide hybrid micelles for enhanced cellular internalization and efficient nuclear drug delivery. Colloids Surf B 181: 315-324.
12. Qu J, Wang R, Peng S, Shi MY, Yang ST, et al. (2019) Stepwise dual pH and redox-responsive cross-linked polypeptide nanoparticles for enhanced cellular uptake and effective cancer therapy. J Mater Chem B 7: 7129-7140.