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Rational Design of Synthetic Polymers as Drug Carriers for Cancer Therapy

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In the latest several decades, we have witnessed the striking development of synthetic polymers as drug carriers from the early issue as implant agents to update various nano-scaled drug delivery systems via transmucosal, oral or intravenous administration. Of these, polymeric nanoparticles delivering anti-cancer drugs, biomacromolecular antibody or genetic substance such as DNA or siRNA to tumor have received predominant attention. In these delivery systems, the polymers play important roles to improve the solubility, regulate the biodistribution, prolong the half-life and control the release of drug, consequently enhanced therapy efficacy and minimized side effect has been expected. By now, quite many polymers have been explored and it has been found that different pharmaceutical formulations would lead to different results. Therefore, the rational design of polymer and formulation, and then the proper combination of both of them is the prerequisite to fabricate a successful drug delivery system. The major method to design optimal polymer can be classified to top-down and bottom-up methods [1]. Bottom-up design methods prepare the polymer derivations on the basis of chemical properties of polymers, while top-down design method is adopted to modify the polymer considering the requirement of cancer therapy. Using bottom-up method, it is easier for chemists to acquire a large quantity of novel polymers, but most of them finally fail to meet the demand of clinical application. On the contrary, top-down method directly aims to clinical application of polymers and the corresponding formulation. With this idea, how to synthesize objective polymer is always the difficulty for those researches working in clinic. Obviously, merging these two methods together is an ideal method to facilitate the development of functional polymers and their transfer from the lab to practical application. Herein, I focus on amphiphilic polymer design for cancer therapy.

Several mature concepts have been built for polymeric nanoparticle mediated drug delivery to passively target tumors based on the enhanced permeation and retention (EPR) effect, active targeting to cancer cells and their suborganelles, and triggered drug release [2]. It has been validated that some basic items including biodegradation behavior, chemical composition, segment length, hydrophobicity, ionization and so on are crucial to the future fate of drug-loaded nanoparticles *in vivo*. Besides, polymer architecture needs to be taken into account. The polymer architecture describes the shape of a single polymer molecule which can be categorized as linear, graft, branched, and cross-linked topology. A well-known linear polymer is N-(2-hydroxypropyl methacrylamide) (HPMA) copolymer [3]. It is a non-toxic water-soluble polymer, and doesn't bind blood proteins without immunity. The unique character of HPMA lies on the molecular structure that there are many active pendant side groups, which can be further modified with drug, targeting residue, and imaging agent and so on. The use of HPMA can avoid rapid RE uptake to assure a long enough circulation time for its accumulation at the tumor site. Then HPMA will deliver anti-cancer drug into cancer cells by the endocytic route. The linkages between polymer and drug have been designed to be stable in the bloodstream and cleaved by lysosomal thiol-dependent proteases. Doxorubicin covalently bound HPMA copolymer was the first synthetic polymer-based anticancer conjugate to enter clinical trial in 1994. Later five other anti-cancer compounds and two gamma camera imaging agents based on HPMA have been evaluated clinically. This concept of functional polymer encourages the advance of biopolymers as drug carriers.

Polyphosphazenes are a typical class of graft biopolymers, which bear two active chlorine side groups on each repeat unit along the biocompatible and biodegradable inorganic backbone. Compared with those popular biomaterials such as polycaprolactone and poly(lactic acid), the distinct advantage of polyphosphazenes for drug delivery is the chlorine side groups on polyphosphazene can be readily substituted by other molecule/macromolecules, therefore, multi-functionalized polyphosphazenes with a variation of physical and chemical characteristics could be obtained. Previously, our group developed a series of thermosensitive amphiphilic polyphosphazenes by introducing N-isopropylacrylamide oligomers for local drug sustained release [4,5]. Recently, our research has focused on amphiphilic polyphosphazenes containing methoxy-poly(ethylene glycol) as hydrophilic chain for tumor targeting treatment. The optimization of hydrophobic sides in amphiphilic polyphosphazenes is a key factor for drug loading in the nanoparticle and drug action with cancer cells as well. For the copolymers containing methoxy-poly(ethylene glycol) and ethyl-*p*-aminobenzoate side groups, the micelle-polymersome conversion was observed when the hydrophilic weight fraction decreased to less than 0.50. This architecture control of polymer self-assemblies provides more possibility to encapsulate various drugs with different physicochemical properties and effectively target them to tumor [6]. Furthermore, we designed a novel amphiphilic polyphosphazene, linked with diisopropylamino side groups, which displayed a sharp pH-sensitive drug release property and the endosomal membrane disruption activities once the nanoparticles trapped in endosome. Furthermore, these pH-responsive nanoparticles have strong potentials to inhibit the growth of drug-resistant tumors [7]. Utilizing this polymer design platform, we can modify polymers step by step to promote their achievement as competent candidates for cancer therapy.

As mentioned above, there are obvious restrictions of polycaprolactone and poly(lactic acid) which cannot dissolve in an aqueous solution and has only one active groups at the end of molecular chain of modification. To overcome this problem, attempts have been made to construct polycaprolactone modification with

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different architectures by copolymerization with other polymers such as poly(ethylene glycol), polyvinylpyrrolidone, and chitosan. Diblock, triblock, graft, star-shaped, hyperbranched copolymers have been reported which can be fabricated in the form of films, microspheres, hydrogels and micelles for cancer therapy [8]. And when hyperbranched polyethylene amine grafted onto the polycaprolactone, the resultant copolymer turns to polyelectrolyte and acquire the capability to complex with DNA or siRNA as a gene vector [9].

To sum up, a comprehensive understanding of the relationship between polymer characteristics and cancer therapy will favor the development of the next generation polymers with precise functions as drug carriers.

References

1. Wang YP, Byrne JD, Napier ME, Desimone JM (2012) Engineering nanomedicines using stimuli-responsive biomaterials. Adv Drug Deliv Rev 64: 1021-1030.
2. Lammers T, Kiessling F, Hennink WE, Storm G (2012) Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. J Control Release 161: 175-187.
3. Duncan R (2009) Development of HPMA copolymer-anticancer conjugates: clinical experience and lessons learnt. Adv Drug Deliv Rev 61: 1131-1148.
4. Zhang JX, Qiu LY, Zhu KJ, Jin Y (2004) Thermosensitive micelles self-Assembled by novel N-isopropylacrylamide oligomer grafted polyphosphazene. Macromolecular Rapid Communitions 25: 1563-1567.
5. Zhang JX, Li XJ, Qiu LY, Li XH, Yan MQ, et al. (2006) Indomethacin-loaded polymeric nanocarriers based on amphiphilic polyphosphazenes with poly (N-isopropylacrylamide) and ethyl tryptophan as side groups: preparation, *in vitro* and *in vivo* evaluation. J Control Release 116: 322-329.
6. Zheng C, Yao XP, Qiu LY (2011) Novel polymeric vesicles with pH-induced deformation character for advanced drug delivery. Macromol Biosci 11: 338-343.
7. Qiu LY, Zheng C, Zhao QH (2012) Mechanisms of drug resistance reversal in dox-resistant MCF-7 cells by pH-responsive amphiphilic polyphosphazene containing diisopropylamino side groups. Mol Pharm 9: 1109-1117.
8. Dash TK, Konkimalla VB (2012) Polymeric modification and its implication in drug delivery: poly-ε-caprolactone (PCL) as a model polymer. Mol Pharm 9: 2365-2379.
9. Liu Y, Nguyen J, Steele T, Merkel O, Kissel T (2009) A new synthesis method and degradation of hyper-branched polyethylenimine grafted polycaprolactone block mono-methoxyl poly(ethylene glycol) copolymers (Hy-Pei-g-Pcl-b-Mpeg) as potential DAN delivery vectors. Polymer 50: 3895-3904.