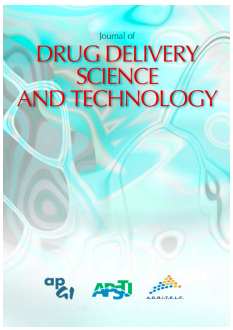

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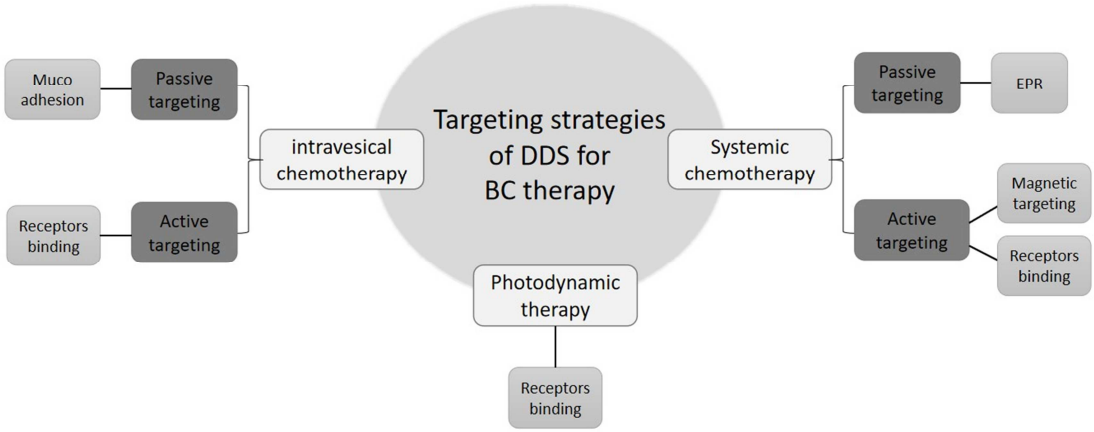

The recent research progress of targeting strategies of drug delivery systems for bladder cancer therapy.

Targeted Drug Delivery Systems for Bladder Cancer Therapy

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Abstract: Bladder cancer is a severe disease that threatens human health. The high recurrence rate and severe side-effects of traditional bladder cancer therapy require more efficient and higher targeting treatment. Drug delivery systems especially being endowed with the targeting property may provide a feasible means to solve such problems. Herein, we have reviewed the recent progress of the drug delivery systems aiming at bladder cancer therapy especially focusing on their targeting strategies. Additionally, we give some outlook of the design on targeting strategy for more effective anti-cancer applications.

Keywords: targeting strategy; drug delivery system; photodynamic therapy; bladder cancer

1. Introduction

Cancer is a category of disease originating from unregulated cell growth and such abnormal cells are able to spread or invade other parts of our body. It is a major public health problem and becomes the second leading cause of death worldwide. Among them, bladder cancer (BC) tops the list of the estimated new cases and deaths [1]. In Europe, BC is the 5th most common cancer type for both sexes affecting rather men than women [2]. In US, BC ranks the 4th most common caner and the 8th in mortality in men [1]. In principle, BC is a rather heterogeneous disease, resulting in a challenge in classification, staging and grading. Generally, 70% of bladder urothelial cell carcinomas represent a superficial disease called nonmuscle-invasive BC, while the other 30% develop a muscle-invasive disease bearing the risk of metastatic spread of the tumor [3]. The standard scheme for superficial BC treatment is surgical transurethal resection with an 80% early success rate. Unfortunately, among them, 70% of those patients develop tumor recurrence within 5 years after surgical transurethal resection [4]. Therefore, chemotherapy still plays an important role in the prevention of tumor recurrence and progression. Although systemic or intravesical chemotherapy using the first-line chemotherapeutic agents (cisplatin, taxanes, gemcitabine, *etc*.) enables long-term survival in some patients, the high recurrence rate and severe side-effects still hinder BC therapy. Thus, more efficient and higher targeting treatment is in urgent need to improve the quality of the BC patients' lives.

Drug delivery systems (DDS) especially being endowed with the targeting property may provide a feasible means to solve such problems, because DDS could offer

increased security, improved stability and enhanced bioavailability of the payloads [5]. Although not frequently used in clinical treatments yet, numerous studies are currently conducted to leverage the potential benefits of DDS for BC therapy [6,7]. And most of those DDS have displayed a favorable therapeutic effect *in vitro* and *in vivo* which hold great potentials in the clinical use. Herein, we have reviewed the recent progress of the DDS aiming at BC therapy especially focusing on their targeting strategies (Figure 1).

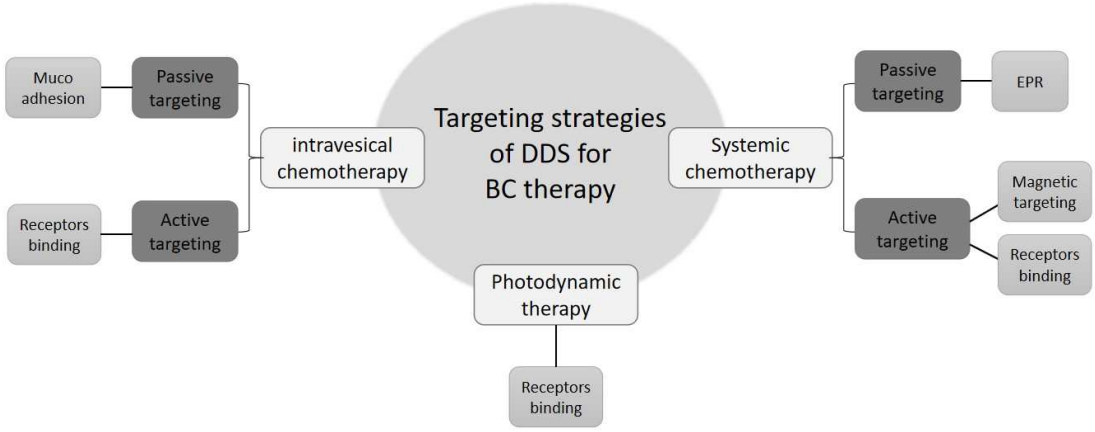

Figure 1. Targeting strategies for bladder cancer therapy

2. DDS for targeted BC treatment

2.1 Systemic chemotherapy

Complete cystectomy has been proven to improve survival rates of BC patients, while the quality of life following cystectomy is pointedly diminished and requires adaptation to a more restrictive lifestyle. And most of BC patients still need chemotherapy after cystectomy to avoid tumor recurrence. Refraining from the severe side-effects causing by the traditional systemic chemotherapy, DDS offer great potential to eradicate BC through a direct injection method. Moreover, such DDS can avert many common problems associated with systemically delivered chemotherapeutics including collateral toxicity to healthy surrounding cells and poor accumulation in the tumor when they are equipped with targeting characters [8].

2.1.1 Passive targeting

Systemically administered therapy for the bladder diseases often fails because only a small fraction of administered drugs reaches the desired site either due to poor absorption or due to losses from metabolism. DDS at the nanoscale are the emergent and promising tools for carrying drugs to targeted site due to the enhanced permeability and retention effect (EPR) of solid tumors [9]. Micelles are the frequently-used carriers. Hu *et al.* [10] used a polymer nanocarrier loaded with lumbrokinase and paclitaxel together to increase the half-life of lumbrokinase and bioavailability of paclitaxel and enhance drug delivery to tumor site through passive targeting. Such DDS significantly inhibited BC growth. Biomimic nanoparticles with homogenous particle size, neutral surface charge and low cytotoxicity were also

employed to delivery drug for BC therapy. The reconstituted high-density-lipoprotein based drug and p53 gene delivery system could targeted delivery both drug and gene to tumor through EPR and simultaneous transfer them to BC cells [11]. Besides, biomimic materials had an advantage at the low biotoxicity. Lysozyme as the drug carrier to delivery doxorubicin for BC chemotherapy showed no renal toxicity [12]. Another biocompatible material used to delivery drug for BC therapy were single walled carbon nanohorns because during their formation, metal catalyst was needless. The requirement for purification and the concern over toxicity could be eliminate [13].

In order to improve the EPR, near infrared radiation could be used for inducing hyperthermia to enhance the permeability of tumor blood vessels, which presumably account for specific targeting of the nanoscale DDS to tumors [14]. So, various near-infrared guided thermal-responsive nanomedicines had been developed [15, 16]. Those nanomedicines could adsorb near infrared radiation and transfer the optical energy to thermal energy to enlarge the intercellular space. And the nanomedicines could enter solid tumor to release drug to inhibit the BC cells through the enlarged gaps between cells.

Nowadays, some researchers claim that EPR is fallacy [17]. However, such viewpoint has not been accepted worldwide. In consideration of the complex physiological conditions in human tumor, unstable tumor interstitial fluid pressure and irregular distribution of blood vessels, the enrichment of nanoscale DDS only depended on EPR may be less effective.

2.1.2 Active targeting

For systemic chemotherapy using DDS, the carriers circulate in the human body. It is of great important to impart the cell-targeting ability to drug carriers. A majority of studies have showed that enabling the DDS with active targeting properties could achieve better therapeutic effect than those DDS based on EPR [18-20]. Among the active targeting strategies, magnetic targeting gains more popularity because of the simple preparation methods, low cost and easy to modification of superparamagnetic DDS [21]. It is well known that iron oxide is a highly biocompatible material for synthesis of superparamagnetic DDS which can be guided to targeted site by the external applied magnetism. Zakaria *et al.* [22] prepared nanoporous iron oxide nanoparticles and applied to the intracellular DDS of BC cells. And the drug delivery efficiency was greatly enhanced by magnetic guiding [23, 24]. The magnetic targeting therapy can significantly improve the intracellular drug concentration. The therapeutic doses can be reduced. The side effects then can be reduced. Additionally, iron oxide holds excellent sensitivity of optical imaging which enables superparamagnetic DDS both diagnostic and therapeutic capabilities. In some animal trials of BC, not only the drug distribution could be longitudinally monitored in vivo, but also the tumors could be imaged through magnetic resonance imaging [25, 26].

DDS surface-functionalized with certain ligands or peptides that selectively target to cancer cells or target proteins on the surface of cell can realize accurately

targeting drug delivery[27, 28]. Wei *et al.* [29] conjugated doxorubicin-loaded polydopamine-modified mesoporous silica nanoparticles with peptide CSNRDARRC targeted to BC cells [30]. And such novel DDS had high targeting efficiency due to specifical recognition. The therapeutic effects on BC were enhanced by the targeting strategy compared with nanoparticles without targeted functional modification. Liu and his co-works [31] had achieved precise drug delivery and the simultaneous inhibition of BC growth, migration and invasion by the linkage of human epidermal growth factor receptor 2 (HER2) antibody on the surface of the nanosystems. The tumor distribution and selective cellular uptake of HER2 conjugated nanosystems were significantly enhanced which greatly contributed to improve the anticancer activities of the loaded drug. Beside, when DDS modified with other peptides (such as PLZ4 [32, 33], Bld-1 [34]) for the systemic chemotherapy also showed excellent performance on precise drug delivery.

These active peptides interact with specific cellular receptors. And they exhibit a good cell adhesive effect which can help DDS in selective targeting for specific cells and tissues resulting in enhanced therapeutic effects and less side effects. However, complex process, low yield, high cost of active peptides still hinder their widely use in clinic.

2.2 Intravesical chemotherapy

Intravesical chemotherapy for BC can avoid systemic uptake of drugs to improve their bioavailability and reduce their side effects. Therefore, intravesical therapy is a valuable option for BC chemotherapy. However, there still needs to figure out some principal challenges of intravesical chemotherapy [35]. Intravesical therapy is inherently limited by the relatively short dwell time of the drug in the bladder, the ability of the drug to penetrate the protective layers of the bladder mucosa, the chemical environment of the bladder (especially pH), and the ongoing dilution of the drug concentration as the urine accumulates in this organ during the treatment period [36]. Hence, the researchers should as far as possible to increase the permeability of drugs through urothelium, prolong the duration of drug action, improve bladder uptake of instilled drugs, reduce the side effect on adjacent normal cells. Advances in nanomedicine have shown great promise in improving the therapeutic efficiency for BC treatment achieved by both passive and active targeting.

2.2.1 Passive targeting

Inadequate drug delivery to tumor cells and dilution of drug concentration by urine production often result in treatment failure in BC intravesical therapy. DDS targeted retention in bladder become much important in intravesical therapy. Some macromolecular polymer exhibit mucoadhesive effect. Lu *et al.* [37] used gelatin nanoparticles to delivery paclitaxel to bladder. Those intravesical paclitaxel gelatin nanoparticles showed low systemic absorption, and favorable bladder tissue/tumor targeting and retention properties in dog's bladder. Besides, chitosan or poloxamer gel and glyceryl monooleate could also be the alternative carriers for intravesical administration of drugs due to their desirable mechanical and bioadhesive effects [38,

39]. And such DDS could increase the residence time of the drugs in the bladder and achieve a more effective intravesical treatment. Using the polyamidoamine dendrimers as the carrier could not only realize target-releasing drug at BC tissue but also show the good performance on high permeability of the urothelium to improve the efficacy of intravesical instillation [40].

Direct instillation of drugs into the bladder is an efficient alternative to systemic delivery, since it reduces side effects, prevents first-pass effects, and consequently allows a more effective treatment. However, this method cannot avoid the drugs uptake by adjacent normal cells. That certainly limits the clinical use of passive targeting intravesical DDS for BC chemotherapy.

2.2.2 Active targeting

Mounting evidence has established that bladder urothelium expresses a host of receptors, which can be leveraged for exclusive therapeutic action in bladder through intravesical drug delivery [35]. As early as 2008, Wirth's team [41] found that lectins could strongly interact with human BC cells and exhibit a high specificity. Such selective cell adhesion could drastically enhance urothelial internalization. Therefore, it was believed that lectin modified DDS might provide a promising tool for intravesical chemotherapy for BC [42, 43]. Based on that, they had prepared various DDS employing different carrier materials (such as poly(lactic-*co*-glycolic acid) [44, 45] poly-ι-glatamic acid [46-48] and bovine serum albumin [49, 50]) conjugated with lectin to realize a biorecognitively drug delivery for intravesical therapy. Those DDS had promising cytoadhesive and cytoinvasive characteristics which could be the auspicious tool to overcome the limiting factors of intravesical therapy to enhanced the treatment effects. And labeling the DDS with fluorescence could enable them not only the diagnostic function, but also a visual performance from binding to uptake. Moreover, using magnetic targeting associated with biorecognitive targeting could get a synergistic effect on drug concentration enhancement at target site [44].

In addition, some specific antigens over expressed surrounding BC cells also can be the targets. Folate receptors have been found expressed in the majority of BC cells [51] which would be of use for targeted delivery of chemotherapeutic drugs. Yu *et al.* [52] prepared polymer micelles linked with folate. The cytotoxicity of targeting DDS was much higher than that of non-targeting ones and free drugs. Besides, the micellar DDS decorated with cyclic (Arginine-Glycine-Aspartic acid-D-Phenylalanine-Lysine) targeting $\alpha_v\beta_3$ integrin [53], hyaluronic acid targeting CD44 [54], the liposome DDS conjugated with RWFV targeting fibronectin [55], and the nanoscale golden DDS linked with a monoclonal antibody targeting glycoprotein [56] all showed strong affinity to BC cells and strong inhibitory effect on BC cells.

The unique structure of the bladder render it a suitable region for intravesical therapy to regional treatment. Modifying DDS with biorecognitive groups makes them specific adhere to cancerous urothelium. Therefore, the treatment effects can be improved and the side effects can be reduced by active targeting intravesical therapy.

2.3 Photodynamic therapy

Photodynamic therapy (PDT) is a form of phototherapy involving photochemistry, photophysics and photobiology. In brief, a photosensitizer (PS) is introduced to the nidi, and then activated by light of specific wavelengths. When there is oxygen around, PS can trigger photodynamic reaction in which produces amount of reactive oxygen species (ROS). Thus, PDT can be a precise regional therapy due to the controllability of the inducing light if the PSs targeted delivery to cancerous site. Similarly, PSs carriers decorated with specific antibody to receptors on the surface of BC cells can realize PSs targeted delivery. Making PSs anchored on the cell membrane could significantly enhance the PDT effect [57]. Hence, all of galactose-binding proteins [58], integrin receptors [59], epidermal growth factor receptor [60, 61], transferrin receptor [62] had been designed as the targets for PSs delivery systems binding. Those PSs delivery systems could uniformly bind to BC cells in short time which was crucial for the clinical application of intravesical treatment. And those conjugates demonstrated rapid cell uptake by receptor-mediated endocytosis. Then they efficiently generated ROS upon irradiation to inhibit the BC cells. The tumor killing efficiency most depends on the PS of which exposure to radiation and production of ROS therefrom. An ideal PS for targeted PDT in clinic should be high singlet oxygen quantum yield, reliable activation by an appropriate wavelength of light, commercial availability [63]. However, most of clinical used small molecular PSs is costly. Besides, PDT is usually used in superficial cancer therapy due to the low penetrability of light. Therefore, the development of more inexpensive but effective PSs (such as zinc oxide which our lab focus on [64]) becomes very important. Another concern for BC therapy using PDT should be expedient radiation exposure to internal PSs. Using the upconversion nanoparticles to transfer the energy of X-ray or near infrared ray which is able to penetrate into human body to PS for ROS production is a promising approach [61, 65, 66] . Therefore, PDT holds a great potential in targeting therapy for BC on the condition that the radiation light could accessibly motivate the cheap and effective PSs.

3. Conclusion and Outlook

This review aims to introduce and discuss the recent researches on the targeting strategies of DDS for BC therapy. In summary, using the targeting DDS can significantly improve the treatment effect and reduce the side effects. Moreover, intravesical targeting therapy is deemed to be more suitable for BC therapy because of the less systemic assimilation, simpler delivery process and more bioavailability. The active targeting strategy can realize more precise delivery compared to that of passive targeting strategy resulting in a more efficient treatment. However, the costly antibody still hinders the widespread use of the active targeting DDS.

Therefore, increasing the therapy efficiency while reducing the costs becomes much important in targeting strategies of DDS for BC therapy. The superparamagnetic nanoparticles are highly biocompatibility and low cost. Besides, their magnetic targeting is attractive [67-69]. Active targeting DDS can mingle with superparamagnetic nanoparticles to gain the magnetic targeting property. Thereout,

less specific antibodies are needed to be conjugated to superparamagnetic DDS. And more targeting efficiency as well as lower cost will be achieved by those two combination targeting strategies.

It seems that PDT would be a precise regional therapy which is fitter for BC treatment. However, the medicinal cost and the penetrability of light also need to be considered. Fortunately, some low-cost PSs are under developing. And the upconversion nanoparticles could utilize more penetrable light to activate PS. It can be inferred that with those problems settled, targeting PDT can become highly applicable in BC therapy.

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Conflict of interest statement

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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