Review Article

Targeted drug delivery via recognition molecules and amphiphilic carriers

Boonchoy Soontornworajit*, Pichayanoot Rotkrua**

Abstract

Advances in targeted anti-cancer drug delivery seem to offer hope in minimizing side effects caused by drug toxicity. Targeted delivery requires specific sites and hydrophobic drug transportation. Each delivery system has to be composed of both recognition molecules and amphiphilic moiety. This review summarizes our current understanding of these two aspects of targeted delivery systems. First, molecular recognition can be achieved by incorporating drugs with molecules that are capable of binding to specific targets (i.e. antibodies, peptides, or small biomolecules). The incorporation could be by means of either direct modification of anti-cancer drugs or modification of drug carriers with recognition molecules. Many studies have demonstrated that the recognition molecules could enhance drug uptake effectively and specifically. Second, in parallel, polymeric materials containing both hydrophilic and hydrophobic segments can be used as the carriers. Examples of amphiphilic materials are amphiphilic polymers, dendrimers, and dendrimer-like star polymers (DLSPs). By coupling recognition molecules and amphiphilic materials, the delivery systems can minimize side effects caused by both anti-cancer drugs and the delivery systems. In addition, the drugs shielded in the delivery system could be circulated in the body for a longer period without a reduction in their activities. Consequently, treatment is expected to be more effective. Overall, targeted drug delivery is a promising tool for application in chemotherapy.

Key words: Drug delivery, Recognition molecule, Amphiphilic carrier, Aptamer, Dendrimer

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* Department of Chemistry, Faculty of Science and Technology, Thammasat University

** Division of Biochemistry, Department of Preclinical Science, Faculty of Medicine, Thammasat University

Introduction

Cancer can be treated by a number of methods, including chemotherapy. However, many anti-cancer drugs for chemotherapy have no specificity for targeting solely cancer cells and consequently, compound patient discomfort. Thus, targeted drug delivery is of widespread interest for anti-cancer drug administration due to its high efficacy and low side effects[1]. Another challenge for conventional chemotherapeutical drugs is that the drugs are hydrophobic and can result in harmful side effects when they are delivered directly in large volumes of aqueous solution[2]. Therefore, it is highly desirable to develop a simple drug delivery system that can improve the water solubility of drugs while retaining their anti-cancer potency, and at the same time minimizing their side effects[3]. The two current challenges in drug delivery include recognizing specific biological sites and delivering hydrophobic drugs.

To achieve targeted drug delivery, one key issue that has to be considered is a specific molecular recognition. Many molecules are capable of binding to specific targets such as antibodies, peptides, or small biomolecules. These molecules exhibit not only specificity but also affinity to their targets. They provide a way to both bring the active drugs to target sites and modulate the drug release[4]. When a certain peptide sequence exhibits molecular recognition to a given target protein under intracellular conditions, they therefore have a potential for use as targeting molecules in drug delivery systems[5]. For instance, a drug delivery system having an anti-HER2/neu peptide, a human epidermal growth factor receptor 2, as its recognition part was able to bring doctexel, an anti-cancer drug, to breast cancer cells effectively[6]. For an application in a controlled-release system, poly (ethylene glycol) (PEG) was functionalized with peptide sequences that are able to specifically bind to basic fibroblast growth factor (bFGF) with a different affinity. Release experiments indicated that the peptide-incorporated PEG could prolong the release of bFGF. In addition, the release rate was correlated with the affinity of the incorporated peptide[7]. This idea based on molecular recognition has been further used for controlled delivery of tumor necrosis factor alpha (TNFα)[8] and anticoagulant hirudin[9] in in vitro and in vivo models.

Another challenge for drug delivery is the effective usage of hydrophobic drugs. In oral administration, the drugs are not effectively absorbed in the target sites due to a loss of the drugs in the digestive tract[10]. Consequently, the bioavailability does not reach a therapeutic window. In intravenous administration, drugs are aggregated, which causes high local drug concentrations and, thus, local toxic effects. The drug aggregation can cause severe side effects such as a respiratory system failure[11]. To overcome these problems, hydrophobic drugs are, therefore, dissolved in clinically acceptable organic solvents such as poly-ethoxylated castor oil, and/or certain surfactants before being suspended in an aqueous phase[12]. In addition, the bioavailability of the hydrophobic drugs can be enhanced using liposomes, microemulsions and cyclodextrins[13 - 15]. However, techniques that rely on the increment of the drug solubility still have some undesirable side effects, such as provoking an unwanted immune response, and require further improvement strategies[16]. Currently, the use of polymeric carriers for delivering hydrophobic drugs is being explored by many researchers. The carriers are amphiphilic blocks or graft polymers consisting of hydrophilic and hydrophobic segments. These have several advantages such as the decrease of the aforementioned unwanted side effects, the increase of drug circulation times, and the reduction of reticuloendothelial uptake[17, 18].

This review only focuses on targeted drug delivery systems that combine the unique properties of recognition molecules and polymeric matrices. Our paper covers types of recognition molecules, applications of recognition molecules, and types of amphiphilic polymers and their applications.

Recognition molecules

2.1 Antibodies

In order to further improve the efficacy of anti-cancer drugs and minimize the unwanted side effects, ligands capable of targeting tumors such as antibodies, peptides, or small biomolecules are directly conjugated to

either the anti-cancer drug or the exterior surface of polymeric vehicles. Antibodies, also known as immunoglobulins, are globular plasma proteins. The immune system produces antibodies to help fight against foreign substances, called antigen. There are five major classes of antibodies with different functions (i.e. IgG, IgA, IgM, IgD and IgE). The most commonly used one is immunoglobulin G (IgG). Antibodies are typically "Y" shaped with natural multivalent nanostructures. The two domains at the tip of "Y" are called the variable region, which allows antibodies to identify and bind only their unique antigens[19]. Thus, antibodies are widely studied in biological and biomedical applications owing to their high binding affinity and specificity[20, 21].

Direct conjugation between antibodies and anti-cancer drugs is a simple strategy to develop drugs with high specificity and potency to cancer cells. This strategy provides the drugs with several advantages, such as a wide therapeutic index, prolonged circulation half-life, and minimal adverse effects[22]. Currently, the United States Food and Drug Administration (FDA) has approved three antibody-conjugated drugs for cancer treatments: Gemtuzumab ozogamicin, Trastuzumab mertansine, and Brentuximab vedotin. Gemtuzumab ozogamicin (Mylotarg) is an anti-CD33 monoclonal antibody conjugated to calicheamicin, a cytotoxic substance. The drug can be internalized upon binding to the CD33 antigen and causes the breakage of DNA inside the leukemia myeloblasts, leading to cell death[23]. Trastuzumab emtansine is composed of the antibody that targets CD340, an epidermal growth factor receptor ErbB protein, and maytansinoid DM1, an anti-cancer agent. This drug is used to treat patients suffering from breast cancer[24]. Brentuximab vedotin is an integration between an anti-CD30 antibody and an SGN-35 drug. This antibody is specific to the tumor necrosis factor receptor superfamily, which is a marker for Hodgkin lymphoma[25]. For the direct conjugation, linkers have to be stable in plasma, and degradable after internalization. The stable linker prevents the drug from being released before reaching the targets, while the degradability permits activation within the target cells. The current linkers are acid-labile hydrazone linkers, disulfide-based linkers, thioether linkers, and β-glucuronide linkers[26 - 28].

Another strategy to develop antibody-based drug delivery is that the antibody can be conjugated to several drug carriers such as liposome, polymeric micelles, and nanoparticles. These carriers possess an intrinsically stealthy surface which can enhance in vivo stability. They are also feasibly prepared with a variety of molecular structures, molecular weights, compositions, and functions so that particular requirements of each drug and application can be fulfilled[29]. For instance, a preparation of antibody-guided liposome for melanoma treatment was modified to enhance the doxorubicin uptake in murine breast cancer treatment[30]. In another example, the availability of anti-epidermal growth factor receptor monoclonal antibody (EGFR mAb) onto the surface of PLGA/poly(vinylalcohol) nanoparticles loading rapamycin enhanced the cellular uptake of malignant breast cancer cells by 17 fold[31].

2.2 Aptamers

Aptamers are single-stranded DNA or RNA sequences identified by the process named systematic evolution of ligands by exponential enrichment (SELEX)[32]. For the first step of the SELEX (Figure 1), a target molecule is incubated with a library containing 10^{12} - 10^{14} DNA or RNA sequences. The incubation results in complexes between bounded sequences and the targets. Then, the unbound sequences are washed from the complexes. Next, the bound sequences are eluted from the complex and further amplified by polymerase chain reaction (PCR). The amplification generates a new library for the next round from amplified sequences. After 6-10 rounds of SELEX, the remaining sequences are able to bind tightly with the target with high specificity and high affinity.

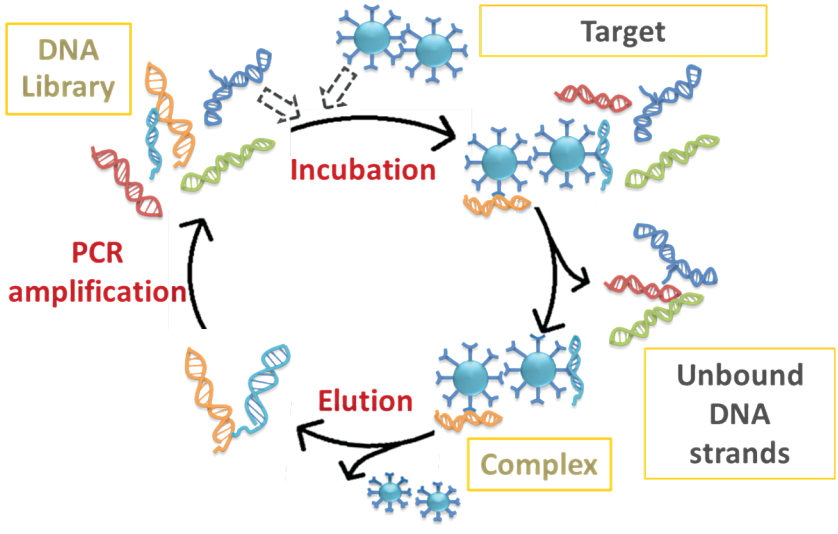

Figure 1 Systematic Evolution of Ligands by Exponential Enrichment (SELEX).

Aptamers have gained significant attention in various research areas as recognition molecules because of their exceptional binding capability[33 - 35]; furthermore, aptamers demonstrate many other desirable characteristics. It is feasible to chemically modify them in order to enhance their robustness in biological environments[33]. For example, it has been reported that aptamers could not be degraded in plasma after the modification by methylation of their ribose structure[36]. Aptamers are relatively small molecules; consequently, they can access hidden epitopes, enabling them to be used more effectively in clinical practice[33]. Another advantage is that the advance technology of solid phase synthesis allows aptamers to be commercially available[33]. The SELEX process provides a way to directly identify the aptamers that can bind to any target molecule[33]. Aptamers show enormous potential in several areas.

Aptamers present a diagnostic advantage because of their high specificity and high affinity. Upon binding to the targets, the conformation of the aptamers change. Subsequently, aptamers are also used as detection molecules. In order to improve detection signals, the concept of the aptamer beacon was introduced. Strategically, aptamers were labeled with chromophores or fluorophores. These types of diagnostic molecules, aptamer beacons, are able to monitor a variety of biomolecules in our bodies[37 - 39]. Meanwhile, coupling aptamers with dye binding assays is an alternative strategy for diagnostic applications. In principle, an aptamer that has a recognition capability is linked to the second aptamer that carries signaling molecules. The recognition part allows the molecule to bind to the desired targets. Then a specific dye is added to the system to label the signal aptamer and emits detection signals. This strategy maintains the molecular structure of the recognition domain because there is no direct modification on the aptamer sequence. To enhance even minimum signals, the specific dye and the signal aptamer could be further modified[40].

The aptamers can be used for therapeutic applications because they exhibit an intrinsic molecular recognition as the antibody. The key advantage of the aptamers over antibodies is the production process. The aptamer production does not require animal subjects; therefore, any types of targets ranging from small molecules to large molecules could be used for identifying aptamer sequences. Aptamers could be used for intracellular, extracellular and cell-surface targets, while other oligonucleotide therapeutics (i.e. antisense oligonucleotide and siRNAs) could be used only for intracellular targets. Thus, aptamers can be used as thera-

peutics in any disease where the extracellular blockade of protein–protein interactions is required. Currently, aptamers are undergoing clinical trials for many diseases: ocular diseases, hematological diseases and cancers[33, 41]. The therapeutic mechanism relies on the inhibition of protein-protein interaction by aptamers as antagonists. In addition, some aptamers work as therapeutic agents in a different way. For example, aptamers that can specifically bind to the extracellular domain of the oligomeric human epidermal growth factor receptor 3 (HER3) can inhibit downstream pathway although their binding sites are different from heregulin, a native ligand[42]. Another aptamer that does not work as an inhibitor is a DNA aptamer that binds to isoleucyl tRNA synthetase. It helps promote the editing reaction in protein synthesis[43]. Generally, as antagonists, the binding affinity between aptamers and their targets play key therapeutic roles[44]. In the case of high binding affinity, it is likely that the therapeutic effect lasts for a relatively longer time. Therefore, two considerations need to be taken into account: 1) high affinity and specificity and 2) a long half-life in the relevant biological compartment to minimize undesired side effects.

2.3 Peptides

Peptide fragments from binding region of antibody have potential for use as recognition molecules in biomedical applications due to their ability to bind to specific molecules[5]. Peptides have several advantages over antibodies including low production cost, large scale synthesis, and low immune stimulation. Moreover, conjugation between peptides and other therapeutic agents is feasible. In addition, the therapeutic agents could maintain their physicochemical properties and bioactivity after peptide conjugation due to relatively small sizes of the peptides. Cyclo (Arg-Gly-Asp) (cRGD) peptide is one example of a small peptide sequence that is capable of binding to $\alpha v\beta 3$ integrin receptors with high affinity. This receptor is overexpressed on both endothelial cells and many types of solid tumors. Therefore, cRGD has demonstrated a potential for use as a molecular guide for anti-cancer drugs. It has also been reported that cyclo(Arg-Gly-Asp-D-Phe-Lys) (cRGDfK), another peptide, was conjugated to PEG-PCL micelles loading doxorubicin (DOX) by post-modification method. Notably, when these therapeutic micelles were treated with $\alpha v\beta 3$ integrin overexpressed SLK tumor endothelial cells, their cellular uptake could be increased by 30 fold[45]. cRGDfK was also coupled with DOX-loaded micelles and superparamagnetic iron oxide to obtain an MRI-ultrasensitive drug delivery system. Thus, the tumor sites could be targeted, labeled and destroyed, simultaneously[46].

2.4 Small biomolecules

Another commercial recognition molecule for targeting tumor cells is folic acid (FA) or vitamin B9. FA has a strong binding affinity to the folate receptor (FR), and this binding can initiate receptor-mediated endocytosis and internalization of FA[47, 48]. FR is frequently overexpressed on the surface of different human tumors, such as cancers of the lung, kidney, ovary and so on, even though its expression on normal cells is low[49, 50]. Moreover, FA is stable, cheap, and non-immunogenic compared to antibodies. Therefore, FA has been widely studied as a promising targeting ligand for cancer diagnosis and therapy[51]. For delivering target-specific paclitaxel (PTX), a common chemotherapy drug, FA-conjugated nanocapsules were prepared by dissolving them in lipiodol and allowed to react with an amine-reactive PEO-PPO-PEO derivative in dichloromethane. The organic phase was subsequently dispersed in an aqueous solution by ultrasonication. PTX was solubilized in the inner lipiodol phase of the nanocapsules. FA possessing enhanced cellular uptake of nasopharyngeal epidermal carcinoma KB cells which overexpressed folate receptors. Then, the PTX caused the cells to be apoptotic[52]. Another example is using biotin, a cell growth promoter, as a recognition molecule. Biotin receptors are often overexpressed on the surface of rapidly proliferating cancer cells. Biotin usage was demonstrated in a study using biotin-functionalized PLGA/PLA-PEG nanoparticles for targeted delivery of PTX[53].

Polymeric candidates for drug delivery

3.1 Amphiphilic polymers

Approaches to delivering hydrophobic compounds using polymeric carriers have been explored by many researchers. Amphiphilic block or graft polymers consisting

of hydrophilic and hydrophobic segments are thought to be good candidates since they can decrease unwanted side effects, prolong circulation time and reduce uptake by the reticuloendothelial system (RES)[17, 18]. Among all these materials, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA) and poly (ϵ-caprolactone) (PCL), and their copolymers with poly(ethylene glycol) (PEG) are the most frequently used biomaterials for drug delivery due to their outstanding biodegradability and biocompatibility[54 - 56]. These amphiphilic copolymers are easily self-assembled in aqueous solution and typically form nanoparticles (NPs) sized from 50 to 500 nanometers (nm) (Figure 2). Recently, an amphiphilic block copolymer comprised of biodegradable photo-luminescent polymer (BPLP), PEG, and cRGD peptide was developed and was able to form a unimolecular micelle NP. The hydrophobic segment worked as a fluorescence signal part. Therefore, the NP is useful not only for hydrophobic drug carriers but also bioimaging applications. cRGD peptides provide a way to target tumor neovasculature and tumor cells specifically[57]. However, the most important limitation for such NPs as drug carriers is their large size, since the particle size of NPs is very important to their in vivo biodistribution[58]. Only small NPs (typically less than 70 nm) can pass through the sinusoidal fenestrations in the liver[59]. Thus, smaller particles can deliver the drugs more effectively because they can avoid spleen sequestration, as well as, they are higher permeable through cells. The quest to develop smaller drug delivery methods is challenging, but a lot of progress is being made.

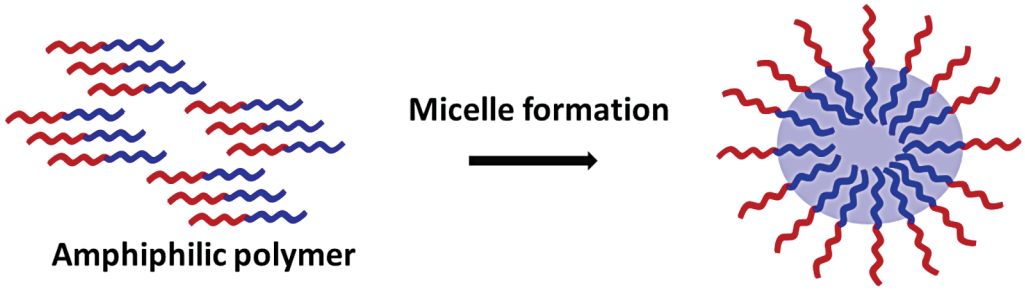

Figure 2 Molecular self-assembly of amphiphilic polymer.

3.2 Dendrimers

Dendrimers are highly branched and symmetrical molecules. They contain a central core, and multiple branches growing up radially from the center like a tree[60]. Compared to block copolymers, dendrimers (Figure 3) possess many unique advantages, such as small particle size (several nm), large numbers of surface functional groups, high surface area-to-volume ratios, and small polydispersity indices (PDI) with a well-defined structure[61, 62]. Therefore, dendrimer-based supermolecules are of widespread interest for many applications such as drug delivery[63], gene delivery[64], tissue sealants[65], molecular encapsulation[66], catalysis[67], and light harvesting[68]. Approaches to delivering hydrophobic compounds are being explored in many laboratories. The large number of surface functional groups allows great opportunities for further chemical conjugation with other molecules, such as targeting molecules, fluorescence or even drugs. For instance, Poly(amido amine) (PAMAM) dendrimer has been modified to carry methotrexate, an anti-cancer drug. Before loading the drugs, PAMAM was functionalized with FA to provide capability of targeted drug delivery. After giving this methotrexate delivery system to tumor-induced mice, the results indicated that the delivery system was effective in treating human KB tumors, which overexpressed the folic acid receptor, as the rate of tumor growth relative to saline-treated mice decreased[69].

In order to effectively use the dendrimers as a drug delivery system, several criteria have to be considered. The structure of the dendrimers lacks amphiphilicity and

they are difficult to be synthesized for high generation. The dendrimers can be synthesized either via a divergent[70] (from core to surface) or a convergent[71] (from surface to core) strategy. These are time-consuming synthesis processes. Moreover, high generation is necessary to obtain unimolecular particles large enough to encapsulate the drugs. Alternative strategies have been developed, including the preparation of segment-block and surface-block dendrimers, and dendritic-linear hybrids[72 - 74]. Amphiphilicity of the dendrimers can be introduced to their structures by inculpating functional groups containing either a hydrophobic or hydrophilic moiety. Depending on the composition and properties of each modification, the functionalized dendrimers are capable of self-assembly and form aggregates in aqueous solution. In order to obtain a small and narrowly distributed particle size, the composition of hydrophobic components needs to be controlled which is unfavorable for drug encapsulation.

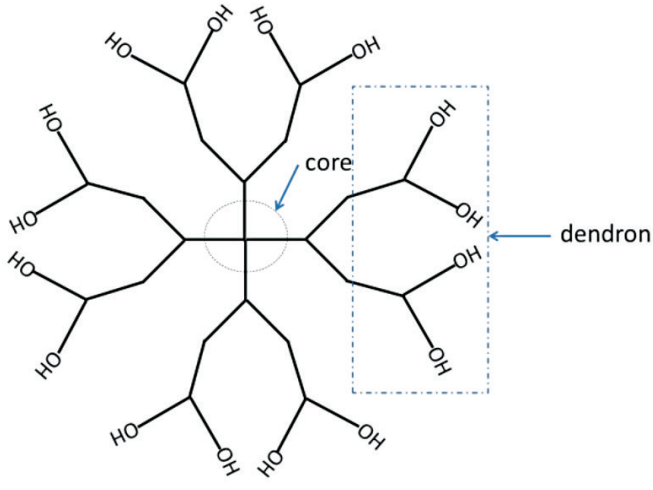

Figure 3 Structural characteristics of dendrimers.

3.3 Dendrimer-like star polymers

Alternative types of macromolecules that can be used for delivering hydrophobic drugs are the amphiphilic dendrimer-like star polymers (DLSPs). DLSPs have structures similar to conventional dendrimers. However, their cores are star-liked polymers instead of low molecular weight moieties[75]. DLSPs could be tuned to have either the polymers as hydrophobic core and dendrons as hydrophilic shells or vice versa. This molecular arrangement provides the following merits. The molecular size can be feasibly tuned by varying the molecular weight of the star-liked polymers. The amphiphilicity is tunable by adjusting the hydrophobic and hydrophilic compositions. With a comparable molecular weight, the overall synthesis of DLSP is easier than that of dendrimers because the DLSPs is initially synthesized from a high molecular weight core; therefore, high generation of DLSPs is not necessary. Comparing to the dendrimers, the increase in a size of the hydrophobic core could provide a space for drug encapsulation. In addition, the peripheral functional groups are allowed to conjugate with other moieties, such as targeting molecules, fluorescence, drugs and so on[76 - 78].

It has been reported that the DLSP comprised of poly(L-lactide) (PLLA) core and PAMMA shell was functionalized by FA, demonstrating the molecular recognition of KB cells[79]. In this study, PLLA was selected as the hydrophobic core owing to its excellent biodegradability and biocompatibility, and an overall synthesis process was followed (Figure 4). First, a well-defined PLLA star polymer was obtained by ring opening polymerization of L-lactide using stannous-2-ethylhexanoate (Sn(Oct)2) as the catalyst. Then a carboxylic acid terminated star polymer was generated by the reaction of succinic anhydride in the presence of N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. A PAMAM

shell with different generations was synthesized using a divergent method resulting in a carboxylic terminated shell. Then, FA was coupled to DLSP via an amide bond using N-ethyl-N-(3-diethylaminopropyl) carbodiimide (EDC), and N-hydroxysuccinimide (NHS) as coupling agents.

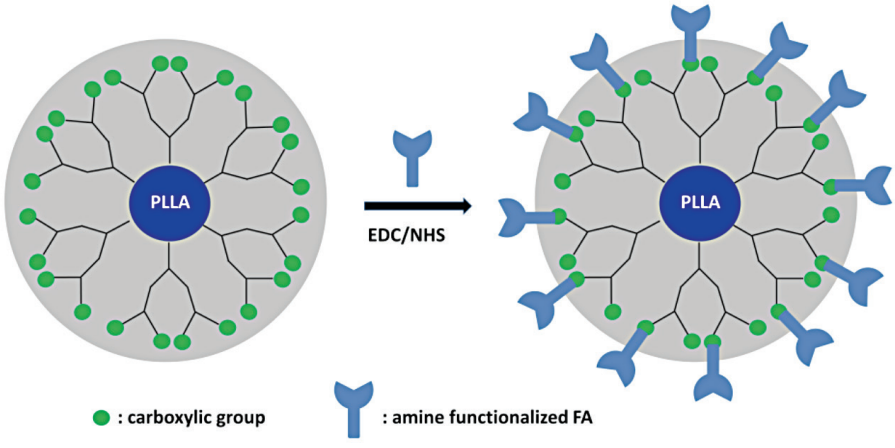

Figure 4 Synthesis of FA functionalized DLSPs for targeted drug delivery.

Conclusion

The development of a drug delivery system that is capable of recognizing target sites is a challenging task in cancer therapy because the existing anti-cancer drugs cause severe side effects. Development strategies rely on the incorporation of several recognition molecules in the delivery system. Promising recognition molecules are antibodies, aptamers, peptide sequences, and some small biomolecules. Upon modification of the delivery system, the anti-cancer drugs could reach target sites efficiently and specifically. Meanwhile, many studies have focused on the encapsulation of anti-cancer drugs in the hydrophobic vicinity of drug carriers: amphiphilic polymers, dendrimers, and DLSPs. The success of encapsulation could provide a way to overcome the toxicity of the anti-cancer drugs in the body. Therefore, a targeted drug delivery system could improve the quality of life for cancer sufferers.

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บทคัดย่อ

การนำส่งยาแบบระบุเป้าหมายโดยอาศัยโมเลกุลจดจำจำเพาะและตัวพายาชนิดแอมฟิฟิลิก

บุญช่วย สุนทรวรจิต*, พิชญานุช รสเครือ**

* ภาควิชาเคมี คณะวิทยาศาสตร์และเทคโนโลยี มหาวิทยาลัยธรรมศาสตร์
** สาขาชีวเคมี สถานวิทยาศาสตร์พรีคลินิก คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

ความก้าวหน้าของระบบนำส่งยาแบบจำเพาะเจาะจงกับเป้าหมายถือเป็นความหวังที่จะช่วยลดผลข้างเคียงจากการใช้ยาต้านมะเร็ง โดยระบบนำส่งยาแบบระบุเป้าหมายจำเป็นต้องมีองค์ประกอบสำคัญสองส่วน คือ บริเวณที่ใช้เป็นเป้าหมายจำเพาะและวิธีการขนส่งยา ยาต้านมะเร็งส่วนมากมักมีคุณสมบัติไม่ชอบน้ำ ดังนั้น ระบบขนส่งยาที่ดี นอกจากต้องประกอบด้วยโมเลกุลจดจำจำเพาะแล้ว ยังต้องมีตัวพายาที่มีคุณสมบัติทั้งที่ชอบน้ำและไม่ชอบน้ำ เพื่อที่จะขนส่งยาผ่านระบบไหลเวียนโลหิตได้ ซึ่งบทปริทัศน์นี้ได้สรุปองค์ความรู้ในปัจจุบันของทั้งสององค์ประกอบดังกล่าว โดยในส่วนแรก จะกล่าวถึง “โมเลกุลจดจำจำเพาะ” ซึ่งเป็นโมเลกุลที่มีความสามารถจับกับเป้าหมายได้อย่างจำเพาะเจาะจง การผสานตัวยาเข้ากับโมเลกุลนี้จะช่วยให้ตัวยาสามารถถูกพาไปยังเป้าหมายได้อย่างแม่นยำ ถูกต้อง ตัวอย่างของโมเลกุลจดจำจำเพาะ ได้แก่ แอนติบอดี เปปไทด์ และชีวโมเลกุลขนาดเล็กเป็นต้น โดยการเชื่อมตัวยาเข้ากับโมเลกุลเหล่านี้สามารถทำได้ทั้งโดยการดัดแปลงที่ตัวโมเลกุลโดยตรง หรือการดัดแปลงที่ตัวพายา มีการศึกษาจำนวนมากที่แสดงให้เห็นว่า โมเลกุลจดจำจำเพาะสามารถส่งเสริมการนำยาเข้าไปในเซลล์ได้อย่างมีประสิทธิภาพและเจาะจง สำหรับในส่วนที่สอง จะกล่าวถึง “ตัวพายา” ซึ่งเป็นวัสดุที่เตรียมมาจากพอลิเมอร์ ประกอบด้วยทั้งส่วนที่ชอบน้ำและไม่ชอบน้ำ ยกตัวอย่างเช่น แอมฟิฟิลิกพอลิเมอร์ เดนไดรเมอร์ และเดนไดรเมอร์ไลค์สตาร์พอลิเมอร์ เป็นต้น จากคุณสมบัติที่กล่าวมาของทั้งโมเลกุลจดจำจำเพาะและวัสดุตัวพายา ทำให้ระบบนำส่งยาแบบจำเพาะเจาะจงกับเป้าหมายนี้ สามารถลดผลข้างเคียงที่เกิดจากทั้งตัวยาต้านมะเร็งเองและวัสดุอื่นๆ ที่เป็นองค์ประกอบในระบบนำส่ง นอกจากนี้ ระบบนำส่งยารูปแบบนี้ยังสามารถช่วยทำให้ยาคงอยู่ในร่างกายได้เป็นเวลานานขึ้น โดยที่ประสิทธิภาพการทำงานของยาไม่ลดลง ดังนั้น จึงทำให้การรักษามีประสิทธิภาพมากขึ้น ถือได้ว่าระบบนำส่งยาแบบจำเพาะเจาะจงกับเป้าหมายได้นำความหวังใหม่มาสู่การรักษาด้วยวิธีเคมีบำบัดสำหรับผู้ป่วยโรคมะเร็ง

คำสำคัญ: การนำส่งยา, โมเลกุลจดจำจำเพาะ, ตัวพายาชนิดแอมฟิฟิลิก, แอพทาเมอร์, เดนไดรเมอร์