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Biopolymers and Peptide Based materials for Targeted Antitumor Drug Delivery: An Overview

Soumi Das[1], Himali Horo[2], Lal Mohan Kundu[1,2]*

[1]*Department of Chemistry, Indian Institute of Technology, India*

[2]*Centre for the Environment, Indian Institute of Technology, India*

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***Corresponding author:** Lal Mohan Kundu, Department of Chemistry, Indian Institute of Technology Guwahati, 781039, Assam, India

Abstract

Targeted antitumor drug delivery seeks to concentrate the antitumor drugs only in the affected tissues sparing the normal tissues, so that the drug efficacy is increased, and side effects are minimized. Various cancer cell targeting moieties are physically immobilized or covalently conjugated to the delivery systems in order to carry the system specifically to the tumour site. This review mainly focuses on the various types of targeting moieties and role of biodegradable polymers and their nanoparticles in site specific delivery of antitumor drugs.

Keywords: Targeted drug delivery; Antitumor drugs; Ligands; Peptides; Biodegradable Polymers; Nanoparticles.

Introduction

Cancer is one of the most common causes of deaths globally. By next 20 years, new cancer cases are likely to increase by 70% [1]. In spite of decades of investigations, the progress in cancer research is still merely incremental. Various antitumor drugs such as Doxorubicin Hydrochloride, Paclitaxel etc, are available but numerous side effects are associated with them [2]. To achieve success in this regard the concept of drug delivery was introduced [3]. From thereon miscellaneous strategies were introduced to eradicate the limitations of the anticancer drugs. This need of delivering the drug specifically to the affected cells sparing the normal cells, unfolded a new research area of targeted drug delivery (TDD) [4]. To accomplish the aim of targeting the cancer cells, researchers considered the difference in cellular micro-environment and compositions between the cancer cells and normal cells. For example, the difference in metabolism profiles, expression of surface receptors, specific position of the diseased cells etc. were considered during the designing of the targeting moiety. The basic idea behind the peptide based targeted anticancer delivery relies on the design of the peptide to selectively target those receptors which are either overexpressed or exclusively present in the cancer cells. The complete delivery system will be comprised of the targeting peptide attached with the drug through a cleavable linker.

The accumulation of a drug only in the affected tissues is accomplished by either or both of the modes of targeting: passive and active. In passive targeting, the physical and chemical properties of the carrier system is modified so that it circulates in the body for longer time and eventually combines with the tumour cells. For example, by alteration of carriers with poly(ethylene glycol) (PEG)/poly(ethylene oxide) (PEO), enhances the solubility of the hydrophobic drugs, increases circulation time and allows specific targeting by improved retention effect and permeability [5]. Whereas, in active targeting, targeting moieties like peptides, proteins (antibodies, transport proteins etc.) and small molecules are used for site specific delivery of antitumor drugs. A drug along with the targeting moieties needs a carrier for its selective, effective and safe administration. Various types of drugs carriers that have been effectively used are liposomes [6], polymers [7], peptides [8], lipids, dendrimers, surfactant etc.[9]. The drugs and targeting moieties are attached to the carriers by various means like adsorption, encapsulation, covalent attachment etc.

Discussion

Some of the most commonly used targeting moieties for targeting cancer cells are discussed here.

Peptides

Peptide carriers are often beneficial compared to other targeting ligands in terms of their easy synthesis and stability towards physical degradation. In addition, peptides can be easily modified for various purposes like increasing solubility, cell penetrability, drug loading etc. Among various peptides designed to target the tumour cells, a tripeptide Arginine-Glycine-Aspartic acid (RGD) gains noteworthy recognition among the researchers. It can recognize αvβ3 integrin along with a family of glycoprotein cell surface receptors also called integrins which are overexpressed in cancer cells, due to their important involvement in tumour progression [10]. Since RGD selectively targets integrins, it became a useful targeting agent for the cancer

cells. It is not only been used to deliver therapeutic drugs but also used in cell imaging [11], nanoparticles [12], liposomes [13] etc. For example, Chen et.al. [14] designed a paclitaxel-dimeric RGD conjugate to deliver paclitaxel in a target specific manner. They have shown improved internalization and localization of paclitaxel in presence of RGD. Not only the integrin, several other receptors such as mammalian bombesin [15], luteinizing hormone-releasing hormone (LHRH) receptors, low level lipoproteins [16], somatostatins [17] were also discovered to target the cancer cells. Various peptides were also designed for the successful recognition of above-mentioned surface receptors and their usefulness were also examined to deliver the drug target specifically. Horvath et. al. designed the peptide GlpHWSYKLRPG -NH2 (Glp = Pyroglutamic acid) to target the LHRH receptors and they have conjugated 2-pyrrolino-DOX with this peptide [18]. They have found the conjugate to completely preserve both cytoxicity of 2-pyrrolino-DOX and binding affinity to the LHRH receptors. Another popular anticancer agent methotrexate was attached with Cyclic fCYwKVCT-NH2 to observe the growth inhibition of MIA PaCa-2 (human pancreatic cancer cells) xenografts in nude mice [19]. Although all these peptide drug conjugates have shown promising results, some details about such delivery systems still require further research. Specially the effect of length of spacer between the drug and targeting peptide on its recognition by the specific receptor as well as its cellular uptake. A notable success was also observed towards targeted drug delivery for the nanoparticle [20], micelles [21] liposomes[13,22] etc. by decorating their surfaces with targeting peptides (Figure 1).

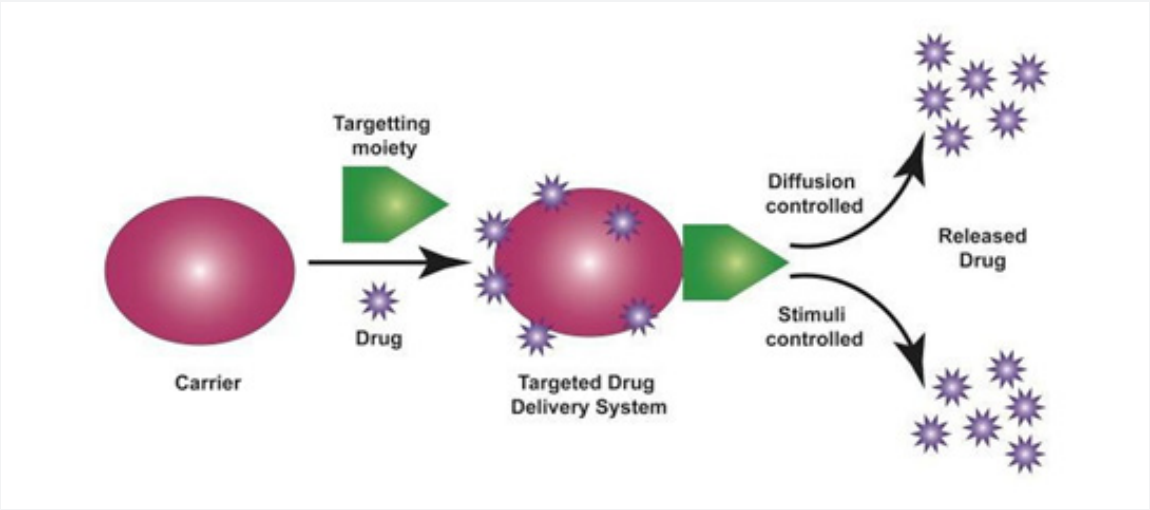

Figure 1: Schematic representation of targeted drug delivery system.

Monoclonal Antibodies and Aptamers

The antibodies as targeting moieties have been widely explored and have been used enormously in treatment applications. Antibodies immobilized species have been used to target antigens that are specifically present on affected cell membranes. Antibody-based drug delivery systems work by identifying specific antigens that are present on the cancer cells and interacts with it. Upon interaction, it induces antitumor affects by various mechanisms [23]. More than sixty five antibody–drug conjugates have been currently in clinical evaluation. For example, Brentuximab vedotin an anti-CD30 antibody-drug conjugate was approved in 2011 which showed proven efficiency in Hodgkin lymphoma and anaplastic large cell lymphoma [24]; Ado-trastuzumab emtansine (T-DM1), an antibody–drug conjugate which was approved in 2013 for HER2-positive metastatic breast cancer [25]. Besides all these peptide and protein based TDD, recently oligonucleotides were also found to be useful to target the cancer cell receptors. Aptamers are oligonucleotides which possess a three dimensional structure, depending on its sequence [26]. Numerous research groups have incorporated synthetic aptamers into the delivery systems. Sangyong et al. [27] have used the A10 2′-fluoropyrimidine RNA aptamer which specifically binds with the prostate-specific membrane antigen (PSMA) present on the prostate cancer cell surface, to form a physical conjugate with Doxorubicin. This formulation was shown to be stable and highly effective to deliver dox specifically to the PSMA expressed cells. Aptamers were also widely utilized to functionalize liposomes [28], nanoparticles [29], polymers and many other nanovehicles to release the payload particularly in the cancer cells.

Small Molecules

Small molecules such as biotin and folic acid have been used as tumour targeting moieties. Folic acid conjugated systems have been widely used, as folate receptors, over-expressed in various types of cancer cells such as ovarian, breast, kidney, cervical, colorectal, lung, and brain tumours [30] rapidly bind to folic acid and triggers cellular uptake via endocytosis [31]. Folic acid conjugated chitosan nanoparticles have been reported for the delivery of 5-fluorouracil, gemcitabine etc. [32]; with silk nanoparticles for the delivery of doxorubicin [31]; with liposomes and peptides for bleomycin, 5-fluorouracil and mitomycin [33]. Similarly, biotin is used as biotin receptors are also overexpressed on tumour cells [34]. It has been used along with various types of organic molecules [35], polymers micelles [36] and polymers nanoparticles [36] for the delivery of doxorubicin and paclitaxel.

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Biodegradable Polymers

Biodegradable polymers have been used in cancer treatment in various forms like nanoparticles [7,37], micelles [37], microspheres [38], etc. With these systems, systemic toxicity and various side effects associated along with conventional cancer therapeutics have been reduced. The chemical and physical properties of the various forms of biopolymers are played around so that they circulate for a prolonged period of time in the bloodstream which is essential for the successful targeted delivery [37]. Biopolymeric nanoparticles have been a promising drug delivery vehicle due to their unique physicochemical properties which enhances the therapeutic and pharmacological properties of the antitumor agents. Moreover, they are biocompatible, biodegradable, have outstanding cell permeability, greater drug-loading capabilities, prolonged circulation time inside body [39]. Chemically modified biopolymers by addition of stimuli responsive linkers [7], targeting moieties such as folate and biotinylated chitosan, silk, alginate, PEG etc. have been used for physical loading or chemical conjugation of the antitumor drugs.

The carboxyl group (-COOH) of folic acid has been employed for covalent conjugation to the amine group (-NH2) of chitosan or silk which gave better stability. Chitosan/PEG blended PLGA nanoparticles are used as long circulating system [39]; chitosan-PEG nanoparticles functionalized with transferrin were used for targeted paclitaxel delivery [40] cyclic pentapeptide cRGDfk and Chlorin e6 (Ce6) conjugated to Silk Fibroin (SF) were used to deliver 5-fluorouracil [41] chitosan succinate/sodium alginate beads encapsulated with capecitabine was used for colon cancer targeted delivery [42].

Conclusion

Drug delivery has become an immensely demanding and rapidly developing field of research. TDD has significant contribution towards the progress of the ongoing anticancer research. However, many of these targeted delivery systems suffer from various limitations. Several limiting issues associated with the systems like their physicochemical stability inside the body, cellular internalization capability, binding property with the receptors, dose dependent release of the cargo etc. need to be addressed intensively. More careful understandings about the existing TDD systems will definitely improve their potency and also the possibility to be marketed as a better chemotherapeutic treatment.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, et al. (2017) Colorectal Cancer Statistics. CA Cancer J Clin 67(3): 177-193.s
2. Thanki K, Gangwal RP, Sangamwar AT, Jain S (2013) Oral delivery of anticancer drugs : Challenges and opportunities. J Control Release 170: 15-40.
3. Allen TM, Cullis PR (2003) Drug Delivery Systems : Entering the Mainstream. Science 303(5665): 1818-1822.
4. You Han Baea KP (2012) Targeted drug delivery to tumours: Myths, reality and possibility. J Control Release 153: 198-205.
5. Van Vlerken LE, Vyas TE, Amiji MM (2007) Poly(ethylene glycol)-modified nanocarriers for tumour-targeted and intracellular delivery. Pharm Res 24: 1405-1414.
6. Torchilin VP (2005) Recent Advances with Liposomes as Pharmaceutical Carriers. Nat Rev Drug Discov 4(2): 145-160.
7. Horo H, Das S, Mandal B, Kundu LM (2019) Development of a photo responsive chitosan conjugated prodrug nano-carrier for controlled delivery of antitumor drug 5-fluorouracil. Int J Biol Macromol 121: 1070-1076.
8. Majumdar S, Siahaan TJ (2012) Peptide-Mediated Targeted Drug Delivery. Med Res Rev 32: 637-658.
9. Mishra N, Pant P, Jaiswal J (2016) Targeted Drug Delivery : A Review Targeted Drug Delivery : A Review. Am J Pharm Res 6:2249-3387.
10. Xiong J, Stehle T, Zhang R, Joachimiak A, Frech M, et al. (2002) Crystal Structure of the Extracellular Segment of Integrin αVβ3 in Complex with an Arg-Gly-Asp Ligand. Science.
11. Lee MH, Kim JY, Han JH, Bhuniya S, Sessler SL, et al. (2012) Direct Fluorescence Monitoring of the Delivery and Cellular Uptake of a Cancer-Targeted RGD Peptide-Appended Naphthylamide Theragnostic Prodrug. J Am Chem Soc 134: 12668-12674.
12. Yang X, Hong H, Grailer JJ, Rowland IJ, Javadi A, et al. (2011) Biomaterials oxide nanoparticles for targeted anticancer drug delivery and PET / MR imaging. Biomaterials 32: 4151-4160.
13. Shi K, Li J, Cao Z, Yang P, Qiu Y, et al. (2015) A pH-responsive cell-penetrating peptide-modified liposomes with active recognizing of integrin α v β 3 for the treatment of melanoma. J Control Release 217: 138-150.
14. Chen X, Plasencia C, Hou Y, Neamati N (2005) Synthesis and Biological Evaluation of Dimeric RGD Peptide - Paclitaxel Conjugate as a Model for Integrin-Targeted Drug Delivery. J Med Chem 48: 1098-1106.
15. Chally ANVS (1997) Design , synthesis , and in vitro evaluation of cytotoxic analogs of bombesin-like peptides containing doxorubicin or its intensely potent derivative , 2-pyrrolinodoxorubicin. Proc Natl Acad Sci 94: 652-656.
16. Firestone RA (1994) Vehicle Antitumor. Bioconjugate Chem 168: 105-113.
17. Sun L, Coy DH (2011) Somatostatin Receptor-Targeted Anti-Cancer Therapy. Curr Drug Deliv 8: 2-10.
18. Nagy, Schally AV, Armatis P, Szepeshazi K, Halmos G, et al. (1996) Cytotoxic analogs of luteinizing hormone-releasing hormone containing doxorubicin or 2-pyrrolinodoxorubicin , a derivative 500-1000 times more potent. Proc Natl Acad Sci 93: 7269-7273.
19. Radulovic S, Szoke B (1992) Cytotoxic analog of somatostatin containing methotrexate inhibits growth of MIA PaCa-2 human pancreatic cancer xenografts in nude mice. Cancer Lett 62: 263-271.
20. Zhang J, Wang L, Chan HF, Xie W, Chen S, et al. (2017) Co-delivery of paclitaxel and tetrandrine via iRGD peptide conjugated lipid-polymer hybrid nanoparticles overcome multidrug resistance in cancer cells. Sci Rep 1-14.
21. Sethuraman VA, Bae YH (2007) TAT peptide-based micelle system for potential active targeting of anti-cancer agents to acidic solid tumours. J Control Release 118: 216-224.
22. Jiang T, Zhang Z, Zhang Y, Lv H, Zhou J, et al. (2012) Dual-functional liposomes based on pH-responsive cell-penetrating peptide and hyaluronic acid for tumour-targeted anticancer drug delivery. Biomaterials 33: 9246-9258.

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23. Jurcic JG, Mulford DA, Scheinberg DA (2008) Monoclonal antibody therapy of cancer, Gen. Princ. Tumor Immunother. Basic Clin Appl Tumour Immunol 321-342.

24. Ansell SM (2014) Blood Spotlight-Brentuximab vedotin. Blood 124: 3197-3201.

25. Lambert JM, Chari RVJ (2014) Ado-trastuzumab emtansine (T-DM1): An antibody-drug conjugate (ADC) for HER2-positive breast cancer. J Med Chem 57: 6949-6964.

26. Keefe AD, Pai SA, Ellington (2010) Aptamers as therapeutics. Nat Rev Drug Discov 9(7): 537-550.

27. Bagalkot V, Farokhzad OC, Langer R, Jon S (2006) An Aptamer-Doxorubicin Physical Conjugate as a Novel Targeted Drug-Delivery Platform. Angew Chem Int Ed Engl 118: 8329-8332.

28. Cao Z, Tong R, Mishra A, Xu W, Wong GCL, et al. (2009) Reversible Cell-Specific Drug Delivery with Aptamer-Functionalized. Angew Chem 48: 6494-6498.

29. Liu J, Wei T, Zhao J, Huang Y, Deng H, et al. (2016) Multifunctional aptamer-based nanoparticles for targeted drug delivery to circumvent cancer resistance. Biomaterials 91: 44-56.

30. Zwicke G, Mansoori GL, Jeffery CJ (2012) Targeting of Cancer Nanotherapeutics. Nano Rev 1: 1-11.

31. Subia B, Chandra S, Talukdar S, Kundu SC (2014) Folate conjugated silk fibroin nanocarriers for targeted drug delivery. Integr Biol (United Kingdom) 6: 203-214.

32. Wang F, Wang Y, Ma Q, Cao Y, Yu B (2017) Development and characterization of folic acid-conjugated chitosan nanoparticles for targeted and controlled delivery of gemcitabine in lung cancer therapeutics. Artif Cells Nanomedicine Biotechnol 45: 1530-1538.

33. Patil Y, Shmeeda H, Amitay Y, Ohana P, Kumar S, et al. (2018) Targeting of folate-conjugated liposomes with co-entrapped drugs to prostate cancer cells via prostate-specific membrane antigen (PSMA) Nanomedicine 14: 1407-1416.

34. Zhao X, Chen J, Chen J, Kuznetsova L, Wong SS, et al. (2010) Mechanism-based tumour-targeting drug delivery system. Validation of efficient vitamin receptor-mediated endocytosis and drug release. Bioconjug Chem 21: 979-987.

35. Pitarresi G, Tripodo G, Calabrese R, Craparo EF, Licciardi M, et al. (2008) Hydrogels for potential colon drug release by thiol-ene conjugate addition of a new inulin derivative. Macromol Biosci 8: 891-902.

36. Chen WH, Luo GF, Lei Q, Jia HZ, Hong S et al. (2015) MMP-2 responsive polymeric micelles for cancer-targeted intracellular drug delivery. Chem Commun 51: 465-468.

37. Deng C, Jiang Y, Cheng R, Meng F, Zhong Z (2012) Biodegradable polymeric micelles for targeted and controlled anticancer drug delivery: Promises, progress and prospects. Nano Today 7: 467-480.

38. Ogura Y, Kimura H (1995) Biodegradable polymer microspheres for targeted drug delivery to the retinal pigment epithelium. Surv Ophthalmol 39.

39. Prabaharan M (2015) Chitosan-based nanoparticles for tumour-targeted drug delivery. Int J Biol Macromol 72: 1313-1322.

40. Nag M, Gajbhiye V, Kesharwani P, Jain NK (2016) Transferrin functionalized chitosan-PEG nanoparticles for targeted delivery of paclitaxel to cancer cells. Colloids Surfaces B Biointerfaces 148: 363-370.

41. Mao B, Liu C, Zheng W, X. Li, R. Ge, et al. (2018) Cyclic cRGDfk peptide and Chlorin e6 functionalized silk fibroin nanoparticles for targeted drug delivery and photodynamic therapy. Biomaterials 161: 306-320.

42. Sinha P, Udhumansha U, Rathnam G, Ganesh M, Jang HT (2018) Capecitabine encapsulated chitosan succinate-sodium alginate macromolecular complex beads for colon cancer targeted delivery: in vitro evaluation. Int J Biol Macromol 117: 840-850.

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