WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 15, 1575-1582. Review Article ISSN 2277– 7105

SITE SPECIFIC TARGETED THERAPEUTICS FOR EFFECTIVE TREATMENT OF CANCER: A MINI-REVIEW

Neelam Sharma, Patel Parita, Shreyas Desai*, Umesh Upadhyay and Bhargavi Rathva

Sigma Institute of Pharmacy, Gujarat Technological University, Bakrol, Vadodara Gujarat India.

Article Received on
21 October 2020,

Revised on 11 Nov. 2020,
Accepted on 01 Dec. 2020

DOI: 10.20959/wjpr202015-19464

***Corresponding Author**
Shreyas Desai
Sigma Institute of Pharmacy, Gujarat Technological University, Bakrol, Vadodara Gujarat India.

ABSTRACT

Cancer is defined by uncontrolled growth of cells and the treatment options available include surgery, radiotherapy as well as chemotherapy. Non-specific distribution of anti-cancer drugs in the body and associated deadly adverse effects limits the use of chemotherapeutic drugs and their effectiveness. Thus, the aim of targeted site specific therapeutics is to deliver anti-cancer drug to the right site of tumour to minimize drug uptake by non-malignant cells. There are two major strategies for targeting know as passive and active targeting. The mini-review describes about both the targeting strategies, mechanisms, challenges, research outcomes and example of such delivery systems for the treatment of cancer.

KEYWORDS: Cancer, chemotherapy, targeted therapy, site-specific, drug carrier, enhanced permeation retention, receptor targeting.

INTRODUCTION TARGETED THERAPEUTICS FOR CANCER

The goal of targeted cancer therapy is to deliver a high dose of an anticancer drug directly to the site of a tumor, to enhance drug uptake by malignant cells, and to minimize drug uptake by non-malignant cells. The general approach for designing targeted cancer therapies is to design the drug delivery system to exploit the features that are unique to tumor cells and tumor tissues. Targeted delivery research has focused on unique features of the tumor microenvironment, such as leaky vasculature, overexpressed cell surface receptors, and intra-tumoral pH differences, as well as features of the cell uptake process, such as endosomal pH. Advances in cancer research in combination with advances in biomaterials and nanotechnology have enabled the development of targeted anticancer drug delivery and a

more tailored approach to treating individual cancer types. The design of an effective targeted therapy will require optimization of therapeutic particles, cancer cell targeting, and drug release mechanisms. Targeting moieties, ligands that bind to receptors overexpressed on malignant cells, can be conjugated to particles to increase cellular uptake, and as a result, enhance treatment efficacy."

Passive targeting

Passive targeting, first described in 1986, takes advantage of the greater vascular permeability and poor lymphatic drainage of tumors that result in the accumulation of micro- and nano-particles in tumor tissue.[1] The particles accumulate through passive diffusion, a phenomenon known as the enhanced permeability and retention (EPR) effect.[2] Enhanced permeability of the EPR effect is the result of the leaky vasculature in tumor tissue. Vessels in tumors are irregularly shaped, leaky, and dilated due to rapid growth and abnormal blood flow.[3,4] Endothelial junctions, gaps in the endothelium that mediate passage of macromolecules from the blood to tissue, vary between non-malignant and malignant tissue. In normal vasculature, endothelial junctions between cells are narrow, ranging from 5 to 10 nm in width,[5] However, in tumor tissue, these junctions range from 100 to 780 nm depending on the tumor type,[6,7] These large gaps allow extravasation of particles out of circulation and into the tumor tissue.

Types of targeting agents

Targeting agents can be broadly classified as proteins (mainly antibodies and their fragments), nucleic acids (aptamers), or other receptor ligands (peptides, vitamins, and carbohydrates). Targeting cancer with a mAb was described by Milstein in 1981.[8,9] Over the past two decades, the feasibility of antibody-based tissue targeting has been clinically demonstrated (reviewed in[10] with 17 different mAbs approved by the US Food and Drug Administration (FDA).[11] Today, over 200 delivery systems based on antibodies or their fragments are in preclinical and clinical trials.[12,13] Recent developments in the field of antibody engineering have resulted in the production of antibodies that are of animal and human origins such chimeric mAbs, humanized mAbs (those with a greater human contribution), and antibody fragments. Antibodies may be used in their native state or as fragments for targeting. However, use of whole mAbs is disadvantageous because the presence of two binding sites (within a single antibody) gives rise to a higher binding avidity. Furthermore, when immune cells bind to the Fc portion of the antibody, a signalling cascade

is initiated to kill the cancer cells. However, the Fc domain of an intact mAb can also bind to the Fc receptors on normal cells, as occurs with macrophages. This may lead to increased immunogenicity — the ability to evoke an immune response — and liver and spleen uptake of the nanocarrier. An additional advantage of whole/intact antibodies is their ability to maintain stability during long-term storage. Although antibody fragments including antigen-binding fragments (Fab), dimers of antigen-binding fragments (F(ab′)2), single-chain fragment variables (scFv) and other engineered fragments are less stable than whole antibodies, they are considered safer when injected systemically owing to reduced non-specific binding.[14,12,15] To rapidly select antibodies or their fragments that bind to and internalize within cancer cells, phage display libraries that involve a high throughput approach may be used,[16,17,18,19] This method generates a multitude of potentially useful antibodies that bind to the same target cells but to different epitopes (a part of a macromolecule that is recognized by antibodies; one receptor may have several epitopes that will be recognized by multiple antibodies). For example, through a selective process, scFv antibodies have been identified for superior binding and internalization properties for prostate cancer cells.[20]'' Targeting moieties are ligands that bind to receptors that are overexpressed on cancer cells Figure 1. Conjugating targeting moieties to the surface of particles promotes uptake and intracellular retention of particles by malignant cells, both of which enhance therapeutic efficacy,[21,22,23,24]

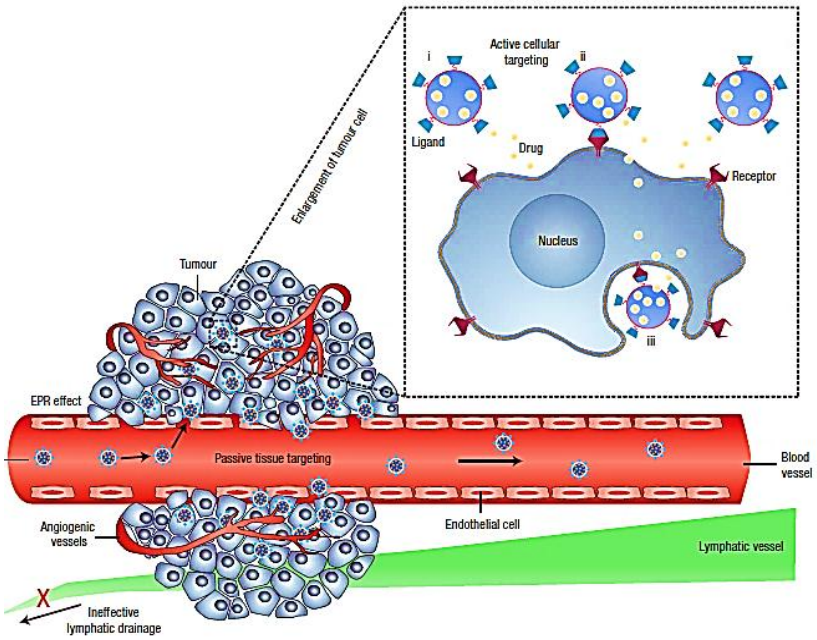

Figure 1: Schematic representation of targeting approach and mechanisms by which nanocarriers (circles) can deliver drugs to tumours.

Active targeting

Active targeting uses ligands to specifically target receptors that are overexpressed on malignant cells. Ligands are molecules, such as folate, transferrin, epidermal growth factor (EGF), and aptamers, which bind to receptors on the surface of a cell. Ligands are conjugated to anticancer drugs or particle-encapsulated drugs to target malignant cells or tumor endothelium. Conjugation is the physical or chemical attachment of a ligand directly to an anticancer drug or attachment to a particle encapsulating an anticancer drug. Ligand candidates for cancer treatment target receptors that are overexpressed on malignant cells. The folate receptor (FR) and the epidermal growth factor receptor (EGFR) are two examples of receptors that are overexpressed on many types of malignant cells. Therefore, conjugation of these ligands to drugs or particles will result in receptor-mediated active targeting and higher drug or particle concentration in malignant cells than in non-malignant cells.[25,26,27,28]

Active targeting promotes internalization of ligand-conjugated drug carriers into a cell via receptor-mediated endocytosis. The lack of tumor selectivity of anticancer drugs and the development of multidrug resistance (*mdr*) have given impetus to the development of target-specific agents and new classes of cytotoxic compounds that may be able to overcome *mdr*.[29,30,31] The drug may be released either at the surface of the cell or upon internalization. The ligand-conjugated particle and receptor are first internalized via invagination, and then an endosome is formed. The anticancer drug must escape the endosome before it fuses with the lysosome to avoid being damaged or destroyed by lysosomal enzymes. After release of the drug and receptor from the endosome, some receptors are recycled back to the surface of the cell where they will be available for another cycle of endocytosis. The active-targeting approach addresses many of the goals for improving cancer therapies. Ligands conjugated to cancer drugs often help protect the cancer drug from degradation and enhance the physical and chemical stability of the drug[32,33,34] Ligand binding also increases the drug dose delivered to malignant cells, which permits systemic administration of smaller doses. Particle internalization that occurs by active targeting has been shown to enhance therapeutic effects[35,36] an important advantage over passive targeting. However, active targeting alone will not achieve optimal results. If an anticancer drug is delivered systemically, the ligand-conjugated drug or drug–particle complex must first reach the cancer tumor before the advantages of active targeting can be realized.[37,8,38]

CONCLUSION

A multidisciplinary approach that includes cancer biology, biomaterials, and nanotechnology has the potential to improve treatment outcomes while minimizing harmful side effects. Passive-targeting mechanisms using the EPR effect are still necessary for extravasation and drug or particle accumulation in tumor tissue. Active targeting promotes internalization of ligand-conjugated drug carriers into a cell via receptor-mediated endocytosis. The use a combination of active and passive targeting in designing drug carriers to improve targeted delivery of cancer therapeutics will serve as a potential alternative for next generation cancer treatment.

REFERENCES

1. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer research, 1986; 46(12,1): 6387-92.
2. Maeda H, Sawa T, Konno T. Mechanism of tumor-targeted delivery of macromolecular drugs, including the EPR effect in solid tumor and clinical overview of the prototype polymeric drug SMANCS. Journal of controlled release: official journal of the Controlled Release Society, 2001; 74(1-3): 47-61.
3. Iyer AK, Khaled G, Fang J, Maeda H. Exploiting the enhanced permeability and retention effect for tumor targeting. Drug Discovery Today, 2006; 11(17–18): 812-8.
4. Vhora I, Patil S, Bhatt P, Gandhi R, Baradia D, Misra A. Receptor-targeted drug delivery: current perspective and challenges. Ther Deliv, 2014; 5(9): 1007-24.
5. Haley B, Frenkel E. Nanoparticles for drug delivery in cancer treatment. Urologic oncology, 2008; 26(1): 57-64.
6. Hobbs SK, Monsky WL, Yuan F, Roberts WG, Griffith L, Torchilin VP, et al. Regulation of transport pathways in tumor vessels: role of tumor type and microenvironment. Proceedings of the National Academy of Sciences of the United States of America, 1998; 95(8): 4607-12.
7. Bhatt P, Vhora I, Patil S, Amrutiya J, Bhattacharya C, Misra A, et al. Role of antibodies in diagnosis and treatment of ovarian cancer: Basic approach and clinical status. J Control Release, 2016; 226: 148-67.
8. Warenius HM, Galfre G, Bleehen NM, Milstein C. Attempted targeting of a monoclonal antibody in a human tumour xenograft system. European Journal of Cancer and Clinical Oncology, 1981; 17(9): 1009-15.

9. Lalani R, Misra A, Amrutiya J, Patel H, Bhatt P, Patil SK. Approaches and Recent Trends in Gene Delivery for Treatment of Atherosclerosis. Recent Pat Drug Deliv Formul, 2016; 10(2): 141-55.
10. Weiner LM, Adams GP. New approaches to antibody therapy. Oncogene, 2000; 19(53): 6144-51.
11. Gabizon AA. Pegylated liposomal doxorubicin: metamorphosis of an old drug into a new form of chemotherapy. Cancer investigation, 2001; 19(4): 424-36.
12. Carter P. Improving the efficacy of antibody-based cancer therapies. Nature reviews Cancer, 2001; 1(2): 118-29.
13. Lalani RA, Bhatt P, Rathi M, Misra A. Abstract 2063: Improved sensitivity and in vitro efficacy of RGD grafted PEGylated gemcitabine liposomes in RRM1 siRNA pretreated cancer cells. Cancer Research, 2016; 76(14): 2063.
14. Allen TM. Ligand-targeted therapeutics in anticancer therapy. Nature reviews Cancer, 2002; 2(10): 750-63.
15. Yewale C, Baradia D, Patil S, Bhatt P, Amrutiya J, Gandhi R, et al. Docetaxel loaded immunonanoparticles delivery in EGFR overexpressed breast carcinoma cells. Journal of Drug Delivery Science and Technology, 2018; 45: 334-45.
16. Patil S, Lalani R, Bhatt P, Vhora I, Patel V, Patel H, et al. Hydroxyethyl substituted linear polyethylenimine for safe and efficient delivery of siRNA therapeutics. RSC Advances, 2018; 8(62): 35461-73.
17. Marks JD. Selection of Internalizing Antibodies for Drug Delivery. In: Lo BKC, editor. Antibody Engineering: Methods and Protocols. Totowa, NJ: Humana Press, 2004; 201-8.
18. Marks JD, Ouwehand WH, Bye JM, Finnern R, Gorick BD, Voak D, et al. Human antibody fragments specific for human blood group antigens from a phage display library. Bio/technology (Nature Publishing Company), 1993; 11(10): 1145-9.
19. Patil S, Bhatt P, Lalani R, Amrutiya J, Vhora I, Kolte A, et al. Low molecular weight chitosan–protamine conjugate for siRNA delivery with enhanced stability and transfection efficiency. RSC Advances, 2016; 6(112): 110951-63.
20. Liu B, Conrad F, Cooperberg MR, Kirpotin DB, Marks JD. Mapping tumor epitope space by direct selection of single-chain Fv antibody libraries on prostate cancer cells. Cancer research, 2004; 64(2): 704-10.
21. Kean A. The present status of radiation therapy in cancer of the ovaries. The American Journal of Surgery, 1935; 27(3): 425-9.

22. Vhora I, Lalani R, Bhatt P, Patil S, Patel H, Patel V, et al. Colloidally Stable Small Unilamellar Stearyl Amine Lipoplexes for Effective BMP-9 Gene Delivery to Stem Cells for Osteogenic Differentiation. AAPS PharmSciTech, 2018; 3550–60.
23. Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discov Today, 2003; 8(24): 1112-20.
24. Lalani R, Misra A, Amrutiya J, Patel H, Bhatt P, Patel V. Challenges in Dermal Delivery of Therapeutic Antimicrobial Protein and Peptides. Curr Drug Metab, 2017; 18(5): 426-36.
25. Bhatt P, Lalani R, Vhora I, Patil S, Amrutiya J, Misra A, et al. Liposomes encapsulating native and cyclodextrin enclosed paclitaxel: Enhanced loading efficiency and its pharmacokinetic evaluation. International Journal of Pharmaceutics, 2018; 536(1): 95-107.
26. Dass CR, Walker TL, Burton MA, Decruz EE. Enhanced anticancer therapy mediated by specialized liposomes. The Journal of pharmacy and pharmacology, 1997; 49(10): 972-5.
27. Buist MR, Kenemans P, Molthoff CF, Roos JC, Den Hollander W, Brinkhuis M, et al. Tumor uptake of intravenously administered radiolabeled antibodies in ovarian carcinoma patients in relation to antigen expression and other tumor characteristics. International journal of cancer, 1995; 64(2): 92-8.
28. Bhatt P, Fnu G, Bhatia D, Shahid A, Sutariya V. Nanodelivery of Resveratrol-Loaded PLGA Nanoparticles for Age-Related Macular Degeneration. AAPS PharmSciTech, 2020; 21(8): 291.
29. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. Journal of Molecular Biology, 1965; 13(1): 238-IN27.
30. Oake A, Bhatt P, Pathak YV. Understanding Surface Characteristics of Nanoparticles. In: Pathak YV, editor. Surface Modification of Nanoparticles for Targeted Drug Delivery. Cham: Springer International Publishing, 2019; 1-17.
31. Chari RV. Targeted cancer therapy: conferring specificity to cytotoxic drugs. Accounts of chemical research, 2008; 41(1): 98-107.
32. Patel J, Amrutiya J, Bhatt P, Javia A, Jain M, Misra A. Targeted delivery of monoclonal antibody conjugated docetaxel loaded PLGA nanoparticles into EGFR overexpressed lung tumour cells. J Microencapsul, 2018; 35(2): 204-17.
33. Mohanty C, Das M, Kanwar JR, Sahoo SK. Receptor mediated tumor targeting: an emerging approach for cancer therapy. Current drug delivery, 2011; 8(1): 45-58.

34. Harsh Trivedi DP, Nandish Pathak. Challenges and future Research in ovarian cancer therapy: A brief Insight. . World J Pharm Sci, 2020; 8(12): 162-6.
35. Iinuma H, Maruyama K, Okinaga K, Sasaki K, Sekine T, Ishida O, et al. Intracellular targeting therapy of cisplatin-encapsulated transferrin-polyethylene glycol liposome on peritoneal dissemination of gastric cancer. International journal of cancer, 2002; 99(1): 130-7.
36. Javia A, Amrutiya J, Lalani R, Patel V, Bhatt P, Misra A. Antimicrobial peptide delivery: an emerging therapeutic for the treatment of burn and wounds. Ther Deliv, 2018; 9(5): 375-86.
37. Straubinger RM, Hong K, Friend DS, Papahadjopoulos D. Endocytosis of liposomes and intracellular fate of encapsulated molecules: encounter with a low pH compartment after internalization in coated vesicles. Cell, 1983; 32(4): 1069-79.
38. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clinical cancer research: an official journal of the American Association for Cancer Research, 2008; 14(5): 1310.