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Review Article

TARGETED DRUG DELIVERY TO CANCER CELLS: ADVANCES IN NANOTECHNOLOGY

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ABSTRACT

Advancement in science and technology has brought a remarkable change in therapy of cancer. Particles are engineered in such a way so that they are attracted to diseased cells, which allow direct treatment of cancer cells. Drug delivery systems control the location in the body where it is released and the rate at which a drug is released. Conventional chemotherapeutic possesses some serious side effects, including damage of the immune system and other various types of organs with rapidly proliferating cells due to non-specific targeting, lack of solubility, and inability to enter the core part of the tumor which results in impaired treatment with the reduced dose and low survival rate. Nanoparticles can be programmed in such a way so that it can recognize the cancerous cells by giving selective and accurate drug delivery avoiding interaction with the healthy cells. The main aim of this review focuses on various strategies for cancer cell targeting. It also discusses specific drug delivery by nanoparticles inside the cells, illustrating many successful researches in the field of cancer therapy.

Keywords: Cancer, Nanotechnology, Targeted delivery, Therapy, Recent advances.

INTRODUCTION

Cancer is a group of diseases that lead to abnormal cell growth that has a high potential to invade other parts of the body [1]. The uncontrolled proliferation of the cancer cells makes treatment process more tedious and more complex. Various methods such as radiation, chemotherapy, removal by surgical methods, and hormone therapy have been employed to treat cancer. It is important to take care that the drugs made for the treatment should have ability to differentiate the cancer cells and normal cells. Hence, in the modern scientific era, the techniques of polymer chemistry and engineering are used to target the specific cancer cells in the body. Conventional chemotherapeutic drugs fail to target the cancer cells selectively. Following reasons provide a brief overview on why conventional chemotherapeutic drugs fail.

- In chemotherapy, the active cancer drugs reach the tumor cells with poor specificity and dose-limiting toxicity.
- When drugs are taken through the oral route, the exposure of the active drug agents may result in disorderly pharmacokinetics, which results in larger than necessary doses that ultimately increase toxicity [2,3].
- Traditional chemotherapeutic agents often get washed out from the circulation being engulfed by macrophages though they remain in the circulation for a very short time and cannot interact with the cancerous cells making the chemotherapy completely ineffective.
- Poor solubility of drugs.
- Chemotherapeutic agents often cannot penetrate and reach the core of solid tumors, failing to kill the cancerous cells.

Nanotechnology is the application of materials, primitive structures, devices, or systems at the molecular, atomic, or macromolecular scales. The nanoparticles size ranges from 1 to 100 nanometre(nm). Nanoscale assays can contribute to cost saving in screening campaigns [4]. Nanomaterials are different from other materials due to the two major factors: The increased surface area and quantum effects. These factors are responsible to enhance the properties such as strength, electrical characteristics, reactivity, and *in vivo* behavior. Few advantages of targeted drug delivery system using nanoparticle is shown in Fig. 1.

Nanotechnology in cancer is being implemented for the diagnosis, detection, and treatment of cancer. It plays an important role in overcoming many of the problems that conventional methods face in the treatment, diagnosis, and detection of cancer [5]. Various research is being carried out to discover more accurate nanotechnology-based cancer treatment and to minimize the side effects of the conventional methods of treatment.

CANCER TARGETING METHODS

The delivery of the drug to the cancer cells can be achieved primarily by two methods - active and passive methods (Fig. 2).

ACTIVE TARGETING

Active targeting is usually achieved by conjugating the nanoparticle to a targeting moiety where chemotherapeutic agents carried by nanoparticles are designed in such a way as they directly interact with the infected cells in the body. Nanoparticles bear some certain functional characteristics. The surface of the nanoparticles consists the essential functional group to bind to target cancer cells receptors. In active targeting, the nanoparticles are designed to target the cancerous cells, either by ligand-receptor interaction or antibody-antigen recognition [6-8]. Polymers, lipids, ceramics, and metals are being currently used to construct the nanoparticles. Natural and synthetic polymers and lipids are typically used as drug delivery vectors [9-11]. Due to the invading nature of our immune system, the nanoparticles carrying the drugs get engulfed by the phagocytes and macrophages. To avoid the engulfing of these nanoparticles, the polymer coating technology has been developed. Polymer contains both hydrophobic and hydrophilic regions. The hydrophilic polymer coating on the nanoparticle surface repels plasma proteins and makes it able to escape from being opsonized and cleared. This is called as a "cloud" effect [12-15].

The active targeting is particularly attractive for the intracellular delivery of macromolecular drugs such as deoxyribonucleic acid, small interfering ribonucleic acid, and proteins. The enhanced cellular internalization rather than an increased tumor accumulation is responsible for the anticancer efficacy of actively targeted nanocarriers. This is the base of the design of delivery systems targeted to endocytosis-prone surface receptors [16].

Receptor targeting

Various nanocarrier with the targeting receptors and targeting ligands along with the type of cancer is given in Table 1. Receptor targeting methods are of various types.

Table 1: Various targets and the respective ligands along with nanocarrier

Nanocarrier	Targets/targeting ligands	Tumor cells	References
Liposomes	Tf receptor/Tf	C6 glioma	[28]
Micelles liposomes	Asialoglycoprotein receptor/lectins, galactosamine	HepG2 B16 melanoma	[29,30]
Liposomes micelles	Folate receptor/folate	Human KB	[31,32]
Liposomes	EGRF receptor/anti-EGRF Mab	MDA-MB-468, U87 glioma	[33]
Magnetic nanoparticles	VEGF/anti-VEGF mAb	Human liver cancer	[34]

VEGF: Vascular endothelial growth factor, mAb: Monoclonal antibody, EGRF: Epidermal growth factor

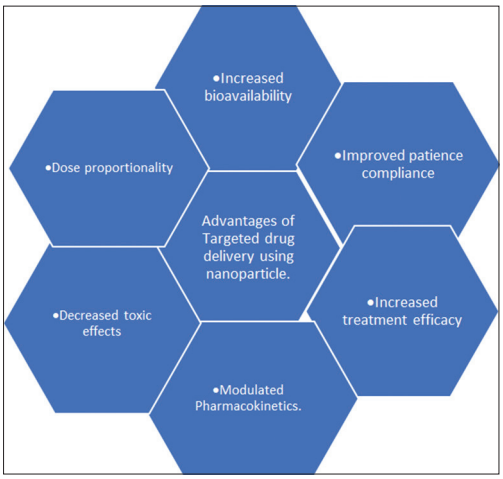

Fig. 1: Advantages of targeted drug delivery system using nanoparticles

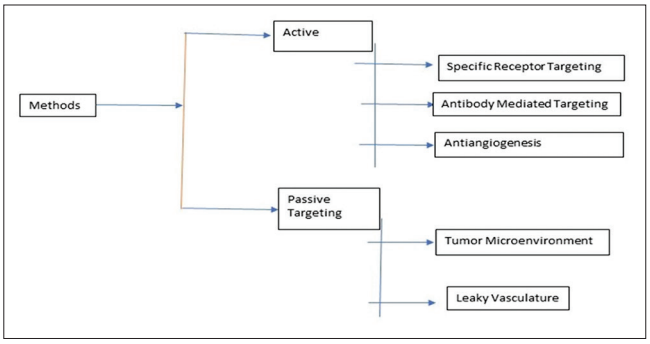

Fig. 2: The active and passive methods of targeting

Epidermal growth factor receptor (EGFR)

It is a transmembrane protein that is a receptor for members of the epidermal growth factor family (EGF family: A family of tyrosine kinase receptors) of extracellular protein ligands [17]. When these receptors get stimulated, they activate the key processes involved in tumor growth and progression, including angiogenesis, invasion, proliferation, and metastasis. Various types of therapeutic approaches are aimed at the EGFR. The EGFR receptors are stimulated when the ligand does not bind to it. The binding of ligand inactivates these receptors which will ultimately lead to cell proliferation. Some of the monoclonal antibody (mAb) inhibitors such as cetuximab and panitumumab help in stopping the binding of receptor-specific ligands to receptors. The mAbs are carried along with nanoparticles (liposomes) to the sites, and it blocks the extracellular ligand binding domain. With the binding site blocked, signal molecules can no longer attach there and activate the tyrosine kinase.

Folate receptor

Folate receptors are responsible for binding of folate (ligand) and reduce the folic acid derivatives and mediate the delivery of tetrahydrofolate to the interior of the cells through receptor-mediated endocytosis. The alpha isoform, folate receptor-α, is overexpressed in 40% of human cancers. In contrast, folate receptor-β is expressed on activated macrophages and also on the surfaces of malignant cells of hematopoietic origin [18]. Utilizing the concept, researchers are designing the surface of nanoparticles with folic acid [19-21]. Russell-Jones *et al*. examined the potential of using folic acid as a targeting agent for the delivery of poly(N-(2-hydroxypropyl) methacrylamide (HPMA) conjugated daunomycin in four murine tumor models. It was found that the tumor-bearing mice injected with daunomycin HPMA conjugates survived more and a number of survivors got increased. The method states that folic acid can be important in enhancing the efficacy of other polymer-bound cytotoxins. Other strategies include:

- Folate-linked methotrexate dendrimers.
- Folate conjugated covalently using surface carboxyl groups as well as conjugation of folate to hydrazine modified polylactic acid nanoparticles (isobutyl-cyanoacrylate nanocapsules used).

The transferrin (Tf) receptor

It is a type of glycoprotein needed for the import of iron into the cell and is regulated in response to intracellular iron concentration. With the increase in the receptor expression, the cell proliferation will be higher. The transferrin receptor that import iron inside the cell is activated in a higher speed that results in greater uptake and leads to rapid cell proliferation which is almost 100 times higher than the normal activation in normal cells. Its extracellular accessibility and ability to internalize and its central role in the cellular pathology of human cancer make this receptor an attractive target for cancer therapy [22-24]. Various approaches have been given by different researchers. Tf can be conjugated to a variety of materials for cancer targeting which include a Tf-chemotherapeutic agent, Tf-toxic protein, Tf-RNases (ribonucleases), Tf antibody, and Tf peptide [25,26]. Similarly, Kawamoto *et al*. worked on Tf -lytic hybrid peptide increased the death efficiency of cancer cells by 80%.

Asialoglycoprotein receptors

The asialoglycoprotein receptors are lectins which bind asialoglycoprotein (glycoproteins from which a sialic acid has been removed to expose galactose residues). Lectins are proteins of non-immunological origin, which have an ability to recognize and bind to carbohydrate moieties attached to glycoproteins expressed on the cell surface. Asialoglycoprotein is overexpressed in hepatoma, which is utilized in cancer targeting using nanoparticles for anticancer drug delivery. Lectins can be incorporated into nanoparticles as targeting moieties that are directed to cell surface carbohydrates [27]. Sung *et al*. prepared poly(--glutamic acid)-poly (lactide) block copolymers loaded with paclitaxel using the emulsion solvent evaporation technique. These nanoparticles inhibited the growth of the cells with a consequent decrease in systemic toxicity.

Antibody mediated

Highly specific mAbs are used to boost up the immune response and to intensify the immune system's antitumor capacity. These types of antibodies target proteins that are abnormally expressed in neoplastic cells. Nanoparticles conjugated with an antibody against a specific tumor antigen are developed for selective drug delivery. Nowadays, hybridoma technology has resulted in the therapy of various diseases. These antibodies are highly specific, and when it is targeted by the drug, it binds to the specific infected cancer cells.

Table 2: Recent strategies for cancer targeting giving positive results

Types of polymer used.	Drug	Targeting agent	Nanoparticle	Results	References
Biodegradable polymer	Docetaxel	Folic acid	Nanoshell	Biodegraded, controlled, sustainable	[50]
PEG-poly (aspartate hydrazone doxorubicin)	Doxorubicin	Folic acid	Polymer micelle	Endocytotic cellular uptake increased	[51]
Poly (D, L-lactide-co-glycolide)	Paclitaxel	Folic acid	Nanopolymer	Inhibition of poly-glycoprotein	[52]
Poly (D, L-lactic acid)	Paclitaxel	mAbs	Polymeric nanoparticle	Selective targeting	[53]
Poly (D, L-lactide-co-glycolide) and polyethylene glycol	Cystatin	Cytokeratin specific monoclonal antibody	Polymeric nanoparticle	Prevent metastasis	[54]

D, L- lactide-co-glycolide: Dextro, levo-lactide-co-glycolide, PEG: Polyethylene glycol, mAbs: Monoclonal antibodies

The hybridoma cell results from the fusion of a myeloma and an antigenically stimulated normal plasma cell to bind specifically to tumor cell antigens. Myeloma cells are used to produce the mAbs. mAbs destroy the cancer cells by the variety of approaches which include directly inducing apoptosis, blocking growth factor receptors, and anti-idiotype formation. It has the ability to totally eradicate cancer cells by activating complement-mediated cellular cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Wartlick *et al*. constructed a biodegradable nanoparticle based on human serum albumin and gelatin in the covalent attachment of the biotin-binding protein NeutrAvidin, enabling the binding of biotinylated drug targeting ligands by avidin-biotin complex formation. Human EGFR 2 (HER2) receptor-specific antibody trastuzumab (Herceptin) was conjugated to the surface of these nanoparticles to target HER2-overexpressing cells. Confocal laser scanning microscopy method showed an effective internalization of these nanoparticles by HER2-overexpressing cells through receptor-mediated endocytosis [35].

Antiangiogenesis

Angiogenesis is the physiological process through which new blood vessels form of pre-existing vessels [36-38]. Angiogenesis is a normal and vital process in growth and development as well as in wound healing. It also helps in the formation of granulation tissue. Cancerous cells produce abnormal amounts of angiogenic growth factors resulting in an excessive angiogenesis overwhelming the effects of natural angiogenesis inhibitors giving rise to leaky and tortuous vessels that are in a constant state of inflammation [39-43].

Inhibition of the vascular endothelial growth factor (VEGF) pathway has become the focus of angiogenesis research. Approximately 60% of malignant tumors express high concentrations of VEGF. During tumor growth, the action of angiogenesis stimulators surpasses the control of angiogenesis inhibitors, allowing for less regulated blood vessel growth and formation.

Active targeting of the tumor vasculature can be achieved by targeting the VEGF receptors with nanoparticles. The first angiogenesis inhibitor for colorectal cancer therapy, bevacizumab (Avastin), an anti-VEGF mAb that inhibits the growth factor of new blood vessels was approved in 2004 [44,45]. Prokop *et al*. constructed a hydrophilic core of sodium alginate, cellulose sulfate, and antiangiogenic factors such as thrombospondin-1 which was cross-linked with dextran polyaldehyde with calcium chloride or conjugated to heparin sulfate with sodium chloride. In addition, bioluminescent agent called luciferase was placed within the polyanionic core. Targeted nanoparticles were evaluated by monitoring luciferase in a murine model.

PASSIVE TARGETING

In passive targeting, nanoparticles accumulate mostly in the neoplastic tissues which result in enhanced permeability and retention (EPR) phenomenon. All nanocarriers use the EPR effect as a guiding principle.

The EPR effect is now becoming the most valuable or we can say the gold standard in cancer-targeting drug designing. Passive targeting consists in the transport of nanocarriers through leaky tumor capillary fenestrations into the tumor interstitium (composed of a collagen network and a gel-like fluid) and cells by convection or passive diffusion [46]. The EPR effect will be optimal if nanocarriers can evade immune surveillance and circulate for a long period. Very high concentrations of drug-loaded nanocarriers can be achieved at the tumor site, for instance, 10–50-fold higher than in normal tissue within 1–2 days [47].

Some limitation of drug during passive deliver to the cancer cells can be:

- The passive targeting depends on the degree of tumor vascularization and angiogenesis [48].
- Thus, extravasation of nanocarriers will vary with tumor types and anatomical sites.
- The high interstitial fluid pressure of solid tumors avoids successful uptake and homogenous distribution of drugs in the tumor [49].

Prevention from lysosomal degradation

Lysosomal enzymes have the capability to destroy both the nanoparticles and drugs inside the cells. When the nanotool usually reach the lysosomal compartment, in which the hydrolytic enzymes are present have the ability to degrade the nanocarrier and the drug carried by the nanocarrier. Therefore, the intracellular distribution of the carrier is modified when the encapsulated drug is a nucleic acid.

Recent studies with different targeting agents, drugs used, and type of nanoparticle

Table 2 gives the various investigations in the field of drug delivery to cancer cells using nanotech methods.

CONCLUSIONS

From the above study, we can conclude that recent methods of drug delivery using nanotechnology methods have enriched the field of medicine in cancer treatment. This has significantly lowered the number of cancer suffering patients in hospitals and reliable cost treatment process with low side effects. The process is highly being used in the selective recognizing of the cancerous cells, targeted drug delivery, and overcoming limitations of the conventional chemotherapies. Various methods are already marketed, and some process is in the phase of clinical trials and research. The two methods active and passive can be used to reduce the disadvantages of chemotherapeutic drugs. Although day by day new type cancers are being found, the nanotechnology can fulfill the wish and hope of patience for living the long life.

CONFLICT OF INTERESTS

The author declares that no conflict of interest occurs during the work.

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