Review Paper:

Nanotechnology: A Way for Active Targeting of Cancer Cells

Sharma Rama
Department of Chemistry, GLA University, Mathura, INDIA
dr.rama76@gmail.com; rama.sharma@gla.ac.in

Abstract

Since cancer is one of the top causes of death, researchers have been working hard for cancer management. Creating drugs that can be utilized for both early detection and efficient treatment, is one of the most challenging parts of cancer treatment. Traditional cancer treatment is linked with a high risk of serious chemotherapeutic side effects and occasionally lacks precise technology for early tumour identification. It was thought that a medication that could serve as a "magic bullet" and could only recognize cancer cells, was required for better therapeutic ratio, defined as the distinction between how treatment impacts cancer cells against healthy tissues.

Nanoparticle systems provide numerous potentially efficient approaches for developing customized cancer detection and treatment medications. There are two methods for targeting nanoparticles: passive targeting and active targeting. Nanoparticles can be effectively localized inside the tumour microenvironment with passive targeting. Due to their active targeting, nanoparticles can be actively taken up by tumour cells.

Keywords: Nanotechnology, Cancer cells, Antibodies, Aptamers, Active targeting, Receptors.

Introduction

Major attempts have been undertaken to enhance the results of cancer management because cancer remains the leading cause of death in people[21]. Despite their high efficacy in killing cancer cells, chemotherapeutics lack precision, resulting in drug-induced harm to non-cancer tissues. Patients who are exposed to nonspecific harmful compounds in treatment paradigms frequently develop significant side effects, which can be life-threatening[44]. At the beginning of the 20th century, Paul Ehrlich introduced the idea of the "magic bullet" into medicine, at least in theory[54]. Since then, researchers from all around the world have been looking for a "magic bullet" that might target cancer cells with extreme precision, facilitating diagnosis and therapy.

Recent developments in cancer nanotechnology have created new avenues for this outstanding platform by a growing class of nanotherapeutics that can directly target cancer cells, providing a significant advantage over conventional therapies[43]. Both passive and active targeting strategies can be used to target nanoparticles.

Targeting using antibodies

Antibodies are a well-known family of target-specific reagents in nuclear medicine that are utilized for diagnostic and therapeutic uses. Antibodies, which were based on antigens found on their surfaces, were the first molecules used to target nano vehicles to certain cell types[5]. Since antibodies have two epitope binding sites on a single molecule, they are extremely selective and have a high binding affinity as targeted therapeutics[27]. It took twenty years for scientists to take into account the possible use of monoclonal antibodies (mAbs) in cancer therapy, even though the first mAb capable of attaching to a specific tumor antigen was created in 1975. Mouse monoclonal antibody Muromonab CD3 (OrthoClone OKT3) was the first mAb to be granted a clinical use license by the FDA[3].

There are already many FDA-approved mAb treatments available and hundreds more are in active trials[4]. The transferrin receptor (TfR), human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR) and prostate-specific membrane antigen (PSMA) are potential targets for mAb-mediated nanoparticle propagation.

Human epidermal growth factor receptor 2 (HER2 receptor): HER2 is only mildly expressed in healthy adult tissues[38], but it is overexpressed in about 25% of invasive breast tumors[28]. Trastuzumab, a humanized monoclonal antibody that targets the HER2 receptor, is now a standard therapy for HER2-positive breast cancer. Due to HER2's high expression on tumor cells, accessibility outside of cells and propensity to internalize following antibody contact, it has been proposed that HER2 should be a target for customized nanoparticle transport to breast cancer. Trastuzumab-conjugated nanoparticles have successfully been shown to target HER2 positive cells in both *in vitro* and *in vivo* studies [46].

Due to its propensity to target just HER2-positive breast cancer cells, this antibody has been utilized to improve radiological identification of breast cancer. Despite the fact that mammography has improved breast cancer early detection, it still misses 10–25% of tumors and is nonspecific for malignancy[16]. As a result, a tumor-specific imaging probe capable of producing a detectable imaging signal from a preclinical malignant tumor would be advantageous. To detect HER2-positive tumors, trastuzumab has been coupled

with super magnetic iron oxide nanoparticles that can be utilized as MRI contrast agents[35]. Tumors that overexpress HER2 receptors had higher signal intensities, which improved cancer detection[56].

Magnetic relaxometry is more accurate than magnetic resonance imaging (MRI) because it exclusively identifies target-bound nanoparticles, even though both techniques can identify and locate targeted magnetic nanoparticles. Hathaway et al[22] employed magnetic relaxometry to find HER2-targeted super magnetic iron oxide nanoparticles. These findings suggest that trastuzumab-conjugated magnetic nanoparticles could be valuable diagnostic tools for breast cancer early detection. Trastuzumab's capacity to target nanoparticles for imaging has also been investigated.

Epidermal growth factor receptor (EGFR): The ErbB receptor family member epidermal growth factor receptor, which is expressed by normal human cells, has been linked to malignancy in a number of epithelial malignancies. EGFR is a possible target for anticancer therapy because cetuximab, a human-murine chimeric monoclonal antibody, binds to it with high affinity and competitiveness[20]. *In vitro* testing with cetuximab has shown that it can successfully and selectively target gold nanoparticles to EGFR-positive pancreatic and colorectal cancer cell lines[8]. The cancerous cells were thermally abated as a result of the heat that the gold nanoparticles produced after being exposed to nonionizing radiofrequency energy.

Cetuximab-targeted gold nanoparticles were studied by Glazer et al[19] in a pancreatic cancer xenograft mouse model. After administering cetuximab-conjugated gold nanoparticles intraperitoneally, tumor xenografts were exposed to radiofrequency, which caused radiofrequency field-induced death of pancreatic cancer xenografts without causing damage to healthy organs. Using an orthotopic pancreatic cancer model, Patra et al[37] evaluated the effects of gold cetuximab-decorated nanoparticles on pancreatic cancer cells that expressed various amounts of EGFR *in vitro* and *in vivo*. These particles carried the anticancer drug gemcitabine, which was their payload. This resulted in a significant *in vitro* and *in vivo* inhibition of pancreatic cancer cell growth in cells overexpressing EGFR.

It has been investigated whether cetuximab can target gold nanoparticles for medicinal as well as cancer detection purposes. When compared to nontargeted gold nanorods, topical injection of gold nanorods precisely targeted to EGFR results in significantly greater image contrast for a skin surface-producing cancer, according to Puvanakrishnan et al[39]. These results show that near-infrared narrow-band imaging can be used to assess and demarcate tumor borders during surgical excision following topical injection of gold nanorods.

When recognizing EGFR-positive A431 cells, EGFR-targeted nanoprobes demonstrated 54 times more specificity and sensitivity than EGFR-deficient MCF7 cells. A new class of smart theragnostic gold nanoparticles that take advantage of the imaging and photothermal capabilities of gold nanoparticles was disclosed by Choi et al in 2012[11]. It has been demonstrated that MRI contrast agents, superparamagnetic iron oxide nanoparticles effectively target cells overexpressing EGFR. Chen et al[7] suggested using MRI imaging of cetuximab-conjugated iron oxide nanoparticles to identify the clinical target volume for radiation treatment and to make a preliminary diagnosis of nasopharyngeal cancer.

According to Kaluzova et al[26], cetuximab-conjugated iron oxide nanoparticles can increase MRI contrast and make glioblastoma cell lines more radiosensitive in both *in vitro* and *in vivo* malignancies. To deliver doxorubicin and superparamagnetic iron oxide to tumor cells that overexpress the EGFR, Liao et al[30] suggested using cetuximab immune micelles. The use of magneto-fluorescent silica nanoparticles attached to cetuximab for *in vivo* imaging techniques to identify EGFR-positive colon cancer was demonstrated by Cho et al[10].

mAbs against EGFR have also been utilized to target the delivery of chemotherapy nanoparticles to cancer cells[15]. These targeted nanocarrier systems could be effective in the treatment of cancers that overexpress EGFR, according to the findings. Cetuximab immune liposomes, according to Chen and colleagues[6], could be employed as a cancer treatment. With a specific goal in mind, a boron delivery vehicle was created. When compared to nontargeted therapy, cetuximab immune liposomes resulted in an eightfold increase in cellular absorption of boron in EGFR-positive glioma cells.

Transferrin receptor (TfR): Given that malignant cells express it at levels several times greater than normal cells, the transferrin receptor is particularly crucial in the creation of nanotherapeutics[13]. In the capillary endothelial cells of the brain, TfR is also present[25]. The blood-brain barrier can be a barrier to the delivery of chemotherapy drugs, hence the transferrin receptor is a potential target for chemotherapeutic drug delivery to malignancies outside the blood-brain barrier[1].

Prostate-specific membrane antigen (PSMA): A tumor antigen called prostate-specific membrane antigen has been found in the neo-vasculature of the majority of solid tumors other than those of the prostate[23]. Sun[48] developed nanoconjugates based on dendrimers that are PSMA-targeted as a platform for specific drug delivery to PSMA-expressing cells. Serda et al[42] examined the anti-PSMA antibody J591 *in vitro* for improving T (1)-weighted MR imaging by targeting LNCaP prostate cancer cells with superparamagnetic iron oxide nanoparticles.

CD20: A novel cancer treatment strategy has been demonstrated to preferentially target lymphoma cells that

overexpress CD20 by combining anti-CD20 monoclonal. In a work by Minai et al[32], anti-CD20 mAb-based drug rituximab was combined with gold nanospheres *in vitro* to transport and release the medication in response to femtosecond laser pulses. The anti-CD20 molecules that were produced, kept their ability to cause complement-dependent cytotoxicity as well as their functionality.

Antibody fragments used for nano construct targeting

It became possible to design and prepare antibody fragments with the advancement of modern antibody technology[52]. The two types of antibody fragments that are most frequently researched for nanoparticle targeting are antigen-binding fragments (Fab) and single-chain variable fragments (scFV)[33]. This method makes it possible to couple numerous targeting peptides to a single nano construct, increasing the targeting efficiency and specificity. This is made possible by the small size of the nanoparticles and antibody fragments.

Each heavy and light chain in the Fab fragments has one constant and one variable domain. Antibody fragments have the same binding selectivity as the whole antibody, but they are nonimmunogenic due to the absence of the Fc fragment's constant domains 2 and 3. As a result, using antibody fragments as a targeting moiety lowers construct uptake by the RES in comparison to entire mAbs and enhances the pharmacokinetic profile of Fab and scFV, as well as nano constructs incorporating them[18]. Antibody fragments are much smaller than monoclonal antibodies (mAbs) which have a molecular weight of about 150 kDa. Antigen-binding fragments have a size of around 50 kDa, whereas scFv have a size of around 25 kDa, which allows for improved penetration into solid tumors[14].

Single-chain variable fragments (scFV): Single-chain antibodies against the prostate stem cell antigen were employed by Ling et al[31] to target the theragnostic polymer nanoparticles containing docetaxel and superparamagnetic iron oxide nanocrystals. In addition to real-time monitoring of the therapeutic effect, these nano constructs were used for concurrent imaging and pharmaceutical delivery. Docetaxel, poly (d,l-lactic-coglycolic acid) and hydrophobic superparamagnetic iron oxide nanocrystals made up the core of the core-shell theragnostic nanoparticles used by Li et al[29]. The shell was composed of two different-sized polyethylene glycol (PEG) molecules and a multilayer of poly allylamine hydrochloride. To specifically transport these core-shell theragnostic nanoparticles to PC3M cells, single-chain antibodies against the prostate stem cell antigen were combined with them[58]; this method is known as targeted delivery.

Antigen-binding fragments (Fab): A number of liposomal nanoparticles containing therapeutic cargo have been targeted using the antigen-binding domains of mAbs in addition to scFV. Doxorubicin-loaded, sterically stabilised liposomes[47], have been linked to a monoclonal antibody that is specific for the human beta1 integrin. Since several beta1 integrins have been found on the surface of human non-small cell lung carcinomas, liposomal nano-conjugates that target them showed tumor-specific binding, efficient incorporation and a significant increase in cytotoxicity when compared with doxorubicin that was not targeted.

Similar to this, doxorubicin-loaded immunoliposomes carrying a Fab of the mAb anti-GD(2), an antibody that targets disialoganglioside, were made using the same technique[36]. These tailored nanoconjugates prevented the growth of cancer cell metastatic spread in all evaluated organs during a metastatic paradigm of human neuroblastoma in nude mice. Drug-loaded immune liposomes were tested *in vivo* and *in vitro* against mAb anti-CD19 or its Fab portions in an animal model of human B cell lymphoma[40].

Antigen-binding fragments were just as successful at delivering the drug vincristine as mAbs, but they had better therapeutic results for the drug doxorubicin. Even though it was more effective than anti-CD19-targeted liposomal doxorubicin, the longer Fab circulation durations were what led to the greater therapeutic efficacy of doxorubicin-loaded immune liposomes. Fab segments from a humanized anti-HER2 mAb were used to target PLGA nanoparticles that were loaded with the PE38KDEL gene. These tailored nanoconjugates have been demonstrated to be more cytotoxic *in vitro* towards breast cancer cell types that overexpress the HER2 gene. These nanoconjugates demonstrated increased therapeutic efficiency in inhibiting tumor growth in a HER2-overexpressing cancer xenograft model when compared to nontargeted controls[41].

Aptamer-based targeting

Since they are twisted into secondary and tertiary three-dimensional structures, aptamers that are single-stranded DNA or RNA oligonucleotides that have the potential to attach to certain biological targets, most typically proteins. Due to their exceptional efficiency as targeting agents, aptamers are sometimes compared to antibodies[34]. "Systemic evolution of ligands by exponential enrichment" (SELEX)[9], an iterative *in vitro* selection process, is used to build aptamers that are selective for a certain target.

Estevez et al[17] coupled aptamers that detect acute leukaemia cells (CCRF-CEM cells) with the system using a dual-nanoparticle system made up of magnetic nanoparticles and fluorescent silica nanoparticles. The preciseness of the detection was confirmed using confocal microscopy and this technology allowed for the identification of as few as 250 cancerous cells.

According to a report, the surface of gold-silver nanorods may covalently bind up to 80 molecules of sgc8c aptamer[2]. It was discovered that the sgc8c aptamer-nanorods had a 26-fold higher affinity for the tyrosine kinase-7 PTK7 transmembrane protein on CCFR-CEM cells than did the sgc8c aptamer without the use of nanoparticles.

According to flow cytometry, CCFR-CEM cells tagged with unconjugated fluorescein-labeled aptamer had a fluorescence intensity signal that was 300 times higher than that of cells labelled with aptamer-nanorods[24]. Taghdisi et al[49] targeted single-walled carbon nanotubes with the same aptamer to achieve pH-dependent daunorubicin release. A similar method was applied by Xing et al[55] to get pH-dependent doxorubicin release from porous hollow magnetite nanoparticles.

Compared to conventional targeted delivery agents like antibodies, aptamers have a number of potential advantages. A good place to start is the fact that aptamers are produced chemically rather than biologically, making them economic to produce and less variable from batch to batch[51]. Additionally, the choice of a broad spectrum of targets including dangerous and nonimmunogenic substances, is made possible by *in vitro* aptamer production. Aptamers are much more resistant to biological degradation and physical stresses like heat, pH and chemical solvents than antibodies[45]. These characteristics of aptamers enable them to withstand the challenging circumstances encountered during nanoparticle production. Aptamers are stable for long-term storage and can be delivered at room temperature following synthesis[50].

Additionally, aptamers degrade slowly and can be repeatedly denatured and renatured without losing their activity[53]. Depending on their backbone, aptamers with functional groups can be modified chemically to yield numerous common synthetic chemistry approaches. A lack of immunogenicity, which can result in higher biodistribution, is an additional benefit of aptamers over antibodies. Finally, although the differences are less obvious when aptamers are compared to antibody fragments[57], aptamers can penetrate solid tumors more deeply than antibodies (10 nm and 155 kDa) due to their smaller size (1-2 nm).

Conclusion

The use of receptors to actively target nanoparticles for distribution holds a lot of promise. For early tumor identification, treatment and even post-treatment monitoring, tumor-targeted nano vehicles are utilized. Additionally, active targeting has made it possible to get through certain obstacles such as the blood-brain barrier and cancer multidrug resistance.

Some of the most significant active targeting techniques that have been researched to date are covered in the current work. In monoclonal antibody-based targeting, whole antibody fragments with exceptional selectivity and binding affinity to their target receptors are employed. However, when used *in vivo*, they did show substantial immunogenicity, which prompted the use of antibody-based fragments like scFv and Fab fragments. These methods are not very immunogenic, which leads to a decrease in RES absorption of nano vehicles and an increase in NP bioavailability. Although aptamers are chemically produced, they are highly durable *in vivo* despite the fact that they are also nonimmunogenic. Additionally, a wide variety of substances, such as poisonous or immunogenic ones, can be developed to serve as their targets. Finally, ligands like transferrin and folic acid have been used to target transferrin receptors and FR- which are overexpressed not just on cancer cells but also on metastatic and drug-resistant malignant cells. Even though some of them have been used in clinical settings, the ideal targeting strategy has not yet been identified. Each offers a unique set of benefits and drawbacks. Perhaps a mix of strategies can be employed to increase the accuracy of medication distribution, enabling more effective customized therapy.

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