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Review article

Site specific nanoparticles for effective treatment of cancer: Basic concepts and strategies

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Abstract

In the recent trend of technology, the nanoparticles provide a new method of cancer drug delivery functioning as a carrier for entry through fenestrations in tumor vasculature allowing direct cell access. These nanoparticles permit exquisite changes for binding to cancer cell membranes. Therefore, the high drug doxorubicin.in addition to this the modification in folate receptor and transferrin receptor leads the cancer treatment by reduced injury of normal cells. By successively addressing each of these barriers, innovative design features can be rationally incorporated that will create a new generation of nanotherapeutics, realizing a paradigmatic shift in nanoparticle-based drug delivery. This extensive survey includes the novel approach of the drug delivery by using nanoparticle will enhance the cancer treatment.

Introduction

In an intravascular or traditional methods of drug delivery system very small amount of the drug reaches to the tumor location and the rest therapeutic factors are spreads in the various locations of the body. The important function of the targeted drug delivery to the specific locations enhance the treatment effects and the maximum amount of the drug is reaches to the tumor site and protect the other organs of the body by preventing the leakage. Therefore, such targeted drug delivery system improves the therapy or treatment efficiency and reduces the side effects of the treatment the active and passive drug delivery systems are generally used as effective targeted drug delivery systems [1].

The nanoparticles are concentrated in the tumor site because of the tumor tissue has leaky vasculature. This advantage of the tumor tissue would be known as enhanced permeation and retention [EPR] [2]. The nano-vectors size is approximately 400nm diameter hence the EPR effects enables transition of this nano vectors in to the tumor tissue area. Therefore, the passive targeting drug delivery systems as mostly depends on the various pathophysiological characteristics of the tumor tissue such as pH, temperature, changes in tumor cell surface and abnormal vasculature [3]. Moreover, in the passive targeting the physicochemical properties such as concentration at targeted cancel site. Also, this technology reduces the toxicity of the normal tissues. There are many drugs are in the clinical trial such as albumin conjugate paclitaxel and liposomal molecular weight, surface charge, hydrophobic, shape and size of the nanoparticles plays significant and crucial role. In addition to this the passive targeting have many limitations like the random nature of targeting, inefficient drug diffusion into tumor cells and very less effect of enhanced permeation and retention in the tumor location but the approach of the passive drug delivery system is interesting [1].

The resolutions of the passive targeting drug delivery system limitation would be satisfied by the active targeting methods through is conjugation of ligands of

tumor with nanocarriers [4]. The monoclonal antibodies and their variable aptamers, peptides, carbohydrates, vitamins and fragments are known as various targeting moiety [5]. In active targeting the biomarkers of the tumor evident that this treatment is over expressed on the tumor cell and provide the efficient and high specificity results. The receptor mediated endocytosis and they released the enzymes through cargo therefore it internalized in the tumor cell. The active targeting is most suitable when the high chances of endocytosis by the tumor cell in comparison to the passive targeting [6], [7]. There are many targeting ligands in the research and development but the some of them are most investigated like transferrin, glycoproteins, epidermal growth factor receptors and folate. The following section is discussed about the different targeting molecules in various active targeting strategies [1].

Nanoparticles for drug delivery in cancer treatment

Recent trend in cancer therapy, specifically in drug delivery has started to evaluate from the traditional practice. This change is required because of the improve chemotherapy drugs therapeutic index. Though, the cancer cells are weaker than the normal cell and give very less effect to the chemotherapy agents. However,this agentaffects to the normal tissues and damage them.The persistence of the cancer cells after the chemotherapy treatment because of the toxicity of the normal cells. Now-onwards efforts are started to kill the cancer cells without damaging the normal cells in the body by using the specific target delivery [8]. To develop such technology more focus on the development of the novel carriers for new and existing drug with proper therapeutic targets agent.

Nanoparticles and nanotechnology

The nanoparticles are constructed and purposely engineered in such a way that measured in nanometer size. The nanoparticle sizes are varied from few nanometers to hundred nm and mostly depends on its use. The nanoparticles can easily pass through the fenestrations of the leaky cancer endothelium. Due to this reason, nanoparticles are used for targeting the tumor at the sites [9, 10].

The lipids, polymers, metals and ceramic materials are used to construct the nanoparticles. The NP have inorganic elements or organic molecules structure. The NP structures have a variety of branched structures, shapes and sizes, tubes, emulsions, liposomes, fullerenes, shells, and spheres [11]. Nanotechnology can provide rapid and sensitive detection of cancer-related molecules, enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. Nanotechnology also has the potential to generate entirely novel and highly effective therapeutic agents.

Targeting drug delivery systems

Passive targeting depends on tumor microenvironment, EPR effect, and tumor pH to deliver therapeutic agents from the nanocarriers. Passive drug targeting is widely exploited in cancer therapy because nanoparticles circulating in the blood stream can localized to cancerous tissues through the well-known Enhanced Permeation and Retention [EPR] effect and helps drugs to expose directly at the tumor tissue bypassing systemic metabolism Anatomically, inherent leaky tumor microvasculature is present in cancerous tissues which is characterized by abnormal branching and enlarged inter endothelial gaps which results in breakdown of tight junctions between endothelial cells and a disrupted basement membrane.

The term “active targeting” defines a cell specific targeting ligand- receptor interaction by coupling with drug or nanocarrier with or without using cross-linking agents at the target site after reaching via blood circulation and extravasation. These targeting moieties have specific affinity for the cell surface antigens [e.g. receptors] and they can differentiate between normal and tumor cells based on the receptor or antigen expression levels. Table 1 indicates the integrins targeted nanoparticles in cancer cells.

Table 1. Integrins targeted NPs in cancer cells.

Integrin	Binding Ligands	Specific Functions in Cancers
α5β1	Fibronectin	Increases tumor progression
	Vitronectin	Increases cancer invasion
αvβ3	Fibronectin	Increases tumor progression
	Vitronectin	Increases lymph node metastasis
	Fibrinogen	Increases bone metastasis
αvβ5	Fibronectin	Increases tumor progression
αvβ6	Fibronectin	Promotes hepatic tumorigenesis
αvβ8	Fibronectin	Is involved in cancer immune evasion

Transferrin receptors

In a body Iron homeostasis factor is an important because its can be play a role in many biochemical processes which can be regulated by the transferrin. The transferrin receptor has nontoxic, biodegradable and non-immunogenic characteristics therefore it can be most viable molecule for the active targeting drug delivery system. The 80kDa molecular mass of the transferrin could be produced by hepatocytes [12]. The table 2 is showing transferrin nanoparticle research and development of different applications. The homodimer molecule as in human transferrin receptor1expressed in the body with different expression levels in nucleated cells. The human transferrin receptor1 are undetectable in non-proliferating normal cells because it acts very fast on cancer cell dividing. Therefore, the affinity of iron-loaded transferrin is 25-fold higher in human transferrin receptor1. TfR has correlations with cancer progression and overexpressed on tumor cell the transferrin is vital section as ligand for tumor targeting [13, 14]. It was observed that the efficiency of drug delivery could be enhanced by the adding the holo-transferrin in Bortezomib-loaded PLGA nanoparticles to pancreatic cancer cells, in vitro. The limitation of the specific drug delivery is blood brain barrier in central nervous system [15].

A proposed mechanism of iron-sensing is that HFE is in complex with TfR1 at low Tf-saturation, but upon increased systemic iron, HFE is displaced by holo-Tf and binds TfR2. Whether HFE-TfR2 complex or HFE in complex with another protein initiates a signaling cascade to induce hepcidin expression is controversial. Signaling then decreases both passively with falling Tf iron saturation and actively through cleavage from the protease matriptase-2. These hypothetical iron-sensing mechanisms are supported by multiple in vitro and in vivo experiments, but mechanisms remain unknown. Though multiple crystal or cryo-EM structures exist for TfR1, little structure-function data has been shown for TfR2. As such, the structural differences between TfR1 and TfR2 that account for the differences in receptor function are unresolved.

Recent development of the transferring coupled nanoparticles are under the clinical trial for its batter effectiveness and efficiency. As per research data transferrin coupled cyclodextrin polymer-based nanoparticles and CALAA-01 of siRNA was the First Target delivery and it is in the phase I. however, to developed a market product of this the transferrin surface modification nanoparticles are in under research.

Cell-penetrating peptides [CPPs]

The Cell-penetrating peptides basically penetrate in to the membrane of the cell and these peptides are short and positive charge. The endocytosis process is used to enhanced the drug delivery in the Cell-penetrating peptides which is showing in to Table 3. There are three groups of Cell-penetrating peptides which is classified as chimeric peptides, derived peptides and proteins. These groups are formed by the combinations of the synthetic Cell-penetrating peptides and two natural sequences [16].

However, to enhanced the efficiency of the Cell-penetrating peptides nanoparticles many in vitro studies were carried out but it was observed that the minimum efficiency was found in in vivo studies. Therefore, Cell-penetrating peptides and ligands combinatory approach may lead the potential in the therapeutic approach in the cancer treatment [17].

Table 2. Various studies of Transferrin coupled Nanoparticles for anticancer applications

Sr.No	Nanoparticles	Cell lines used for study	Research Outcome
1.	DOX-lipid-coated PLGA-Tf	A549 tumor-bearing mice	The lung cancer tumor growth can be cured nude mice in vivo.
2.	DOX-PAMAM-PEGT7/ ADR-Tf	Bel-7402 tumor bearing nude mice	The higher cellular uptake and lesser IC [50] following Tf functionalizing, in vitro and in vivo.
3.	DNA-liposome-Tf	DU145 prostate cancer model	Tf-lipoplex exhibited high stability, gene transfer efficiency, and long-term efficacy for systemic p53 gene therapy, in vitro and in vivo
4.	PEG-PLA-micelle-Tf	Intra-cranial rat tumor model of C6 glioma	Cellular uptake of the Tf–PEG-PLA micelles was significantly higher than non-targeted micelles, in vitro and in vivo.
5.	Diphtheria toxin-Tf mutants	HeLa	Site-directed mutagenesis in Tf provides an alternative method for improving the drug carrier efficacy of Tf, in vitro.

Table 3. Various Studies on Cell-penetrating peptides nanoparticles.

Sr. No.	Nanoparticles	Cell lines used for study	Research Outcome
1.	PEG-LA-Penetratin	MDCK-MDR model	Penetratin conjugated NPs exhibited a significantly enhanced brain uptake and reduced accumulation in the non-target tissues, in vitro and in vivo.
2.	TAT-Dextran-SPION	Murine lymphocytes and activated human NK cells	TAT-modified particles were internalized into lymphocytes more efficiently than non-modified particles, in vitro
3.	TAT-Dextran- liposome	Calu-3	TAT-conjugated NPs localize for the most part in the cytoplasm with only a small amount of nuclear localization, in vitro.
4.	TAT-modified liposome [TAT-LIP]	Brain capillary endothelial cells [BCECs] of rats	TAT-LIP was a promising brain drug delivery system due to its high delivery efficiency across the BBB.
5.	TAT-DOX- chitosan	BALB/c mice bearing subcutaneous tumors	TAT- targeted NPs could effectively decrease tumor volume, in vivo.

LDL-LDL receptor

There are five types of lipoproteins categorized based on densities, such as chylomicrons, very low-density lipoproteins [VLDL], intermediate density lipoproteins [IDL], low-density lipoproteins [LDL], and high-density lipoprotein [HDL]. The phagocytic system cannot distinguish lipoprotein due to their endogenous nature. Lipoprotein transports cholesterol, and other lipids in the blood, in which Apolipoprotein B-100 cover about half of the LDL surface area targets the LDL to LDL receptors [LDLRs] in several tissues, such as liver, adrenal glands, and ovaries. It has shown high expression of LDLRs on BBB, LDL can be used as the effective targeting molecule for drug delivery into CNS. Hematoporphyrin [HP] is a potent photosensitizer for photodynamic therapy which can be bind to LDLRs on the tumor cell membrane [18].

Integrins and integrin ligands

Integrins are composed of heterodimers of α and β chains. It has been demonstrating 24 different integrins which are overexpressed in cancers and can enhance disease progression in part through angiogenesis and metastasis. The study showed that DOX-loaded cRGD-conjugated unimolecular micelles exhibited better uptake by U87MG human glioblastoma cells and higher accumulation in tumor site compared to non-targeted NPs. The investigation demonstrated polyglutamic acid-PTX-E-[c[RGDfDK] [2] NPs could potently inhibit angiogenesis process in part through the suppression of the growth of proliferating αvβ3 expressing endothelial cells and tumor cells. It has evidence to target potential of integrin-ligand coupled NPs depends on the number of conjugated ligands [19, 20]. Integrins are transmembrane receptors that facilitate cell-extracellular matrix [ECM] adhesion because as integrin ligands are typically massive and well cross-linked components of the ECM.

Carbohydrates [Lectin ligands]

Remarkably shown glycan group on the cell surface play a significant role in various physiological actions, including cell-cell and cell-substrate interactions, immunogenicity and protein targeting. In addition, during various pathologic condition, such as cancers may modify their structures to lead to the generation of tumor-associated carbohydrate antigens [TACAs]. TACAs are very important molecules for cancer progression processes such as metastasis, advised to binding of surface carbohydrates with their ligands [lectins] leads to accumulation of glycans inside the cells in part through endocytosis process. The study observed that galatose based hepatocyte asialoglycoprotein receptor [ASGP-R]ligands [arabinogalactan and pullulan] showed high affinity to ASGP-R compared to the glucose-based polymer [kappa carrageenan] in hepatic targeted NP-mediated curcumin delivery. Carbohydrate-based active targeting studies show that they are potent targeting moieties for anti-cancer drug delivery. Nevertheless, the wide spectrum expression of their ligands on normal cells forces us to perform more studies before their application in trials [21].

Folate receptors

Folic Acid [FA, or Vitamin B9] is an essential nutrient which is responsible for the synthesis of purines and pyrimidine. The high-affinity folate receptors [FRs] is a mediator to transport Folic Acid to the cells in a non-destructive, recycling endosomal manner. It has characteristics of the low expression of FRs on healthy tissues and their over expression on cancer cells. Consequently, it is advantageous targeting molecule for active drug delivery to tumor cells. Many studies are demonstrating the coupling of albumin NPs with FA significantly increase site-directed drug delivery in cancer cells. FA targeted NPs can remarkably target FR-expressing cancer cells, measured as a useful weapon for cancer imaging and treatment [22-24].

Conclusions

Observing the extensive survey of the drug delivery for the cancer treatment, the novel approach of the nanotechnology has ability to overcome convectional cancer treatment limitations by targeting the cancer cell and protecting the healthy tissue. In forthcoming future, the development of the nanoparticle technology and cancer chemotherapy delivery treatmentwill expand effectively cancer treatment. The novel ligands, new tumor targets, particle stabilization and new strategies for targeting will enhance the target delivery and decreased the toxicity to the normal tissues. Nanoparticles have many morecapabilities including uses in imaging and sensing, diagnosis, targeting, radiotherapy, and transport of genetic material.

The future of nanomedicines requires collaboration among researches, industry, and regulatory agencies to ensure that safe and effective nanomedicines will be produced in sufficient quantity and quality to meet the demands of society, providing rapid access to both innovative, reliable, and efficacious treatment options.

Author contributions

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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