IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023

A Review on Tumour Specific Drug Delivery System

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Abstract: *With the development of nanomaterials, the study of drug delivery systems has exploded into a new field of cancer care in recent years. Drug delivery systems such as drug nanoparticles (nps) are expected to have more advantages in antineoplastic outcomes than conventional antitumor drugs, such as simple assembly, high efficiency, low toxicity, and in particular, active tumor-targeting ability. Delivery carriers, antitumor drugs, and even target molecules are the most common form of drug delivery. There are no systematic reviews on a list of drug delivery protocols used for tumor treatment at the moment. This paper introduces the design, functions, and applications of many common delivery carriers, as well as the antitumor mechanism of various antitumor drugs in delivery carriers in detail, providing a more theoretical basis for the future use of personalized cancer nanomedicine in the clinic.*

Keywords: drug delivery system, delivery providers, antitumor drug, targeting, tumor therapy

I. INTRODUCTION

The number of effective cancer therapies has dramatically increased in recent decades, owing to our improved knowledge of carcinogenesis mechanisms, cell biology, and the tumor microenvironment. Despite the significant investment in preclinical and clinical research, many cancers are still fatal. The targeted delivery of anticancer drugs is one of the ways to raise the survival rate of cancer patients. Recent advances in biomedical science and biotechnology have resulted in the identification and production of effective drug carriers such as liposomes, dendrimers, and gold and magnetic nanoparticles. their suitability for the development of technologies for targeted drug delivery to specific tissues, cells, and even intracellular organelles is the key difference between these new forms of formulation and classical ones. The essence of targeted delivery lies in the surface of a drug container (carrier) that contains a modified drug or molecule with a functional group that can be recognized by the target cell receptors. Folic acid removal is a common example because it is actively taken up by tumor cells. Antibodies and aptamers are universal proteins that recognize the surface of a target cell. The antigenic portraits of cells are becoming more detailed as a result of advances in basic biomedical research, allowing us to distinguish one cell from another based on their surface characteristics. Medicines that are administered orally or parenterally are distributed throughout the body, with only a small amount reaching the intended area. Hence, targeted delivery schemes make it possible to reduce the dose of an administered drug and minimize its effect on other cells, which is very important in chemotherapy because drugs are highly toxic. The presence of recognizing or recognizable molecules on the surface of a delivery system allows it to concentrate on the desired area. It is also vital that the delivery system penetrates the cell and that the drug is then delivered to the nucleus, mitochondria, endoplasmic reticulum, and other organelles. In fact, the concept of intracellular drug delivery is still in the works. To ensure safe intracellular transport, one must know the signaling pathways that link proteins to different cellular structures. More detail is needed about the cell's motor proteins, which directionally move loads over long distances.

II. DRUG DELIVERY SYSTEMS

drug delivery systems are devices that transport drugs into or through the body. These technologies include the method of delivery, such as a tablet you swallow or a vaccine that is administered. Types of drug delivery method a novel drug delivery scheme is a novel way to deliver drugs that transcends the limitations of traditional drug delivery methods. A novel drug delivery system (ndds) is a term used to describe the development of new pharmaceutical forms with optimized properties such as smaller particle size, higher permeability characteristics, and selective site targeting.

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Microparticles,nanoparticles, liposomes,niosomes,transdermal drug delivery, microencapsulation targeted drug delivery method to reduce the atypical toxic effect of conventional drug delivery by defining the drug moiety specifically into its target body area (organic, cellular, and subcellular level of specific tissue), targeted drug delivery is a method of lowering the amount of drug required for therapeutic effectiveness.

- Polymeric micelles
- Liposomes
- Lipoprotein based drug carrier
- Nano particle drug carrire
- Dendrimer

The benefits of the drug delivery system:

1 Many diseases can be treated with greater precision (e.g. aspitballl)
2 Bioavailability has been improved
3 The frequency and severity of potentially harmful systemic side effects associated with high blood plasma drug concentrations have been reduced.
4 Better patient compliance effect.
5 Biocompatibility.
6 Targeting the drug molecule towards the affected tissue or organ make less chances of toxicity.

Limitations:

Physiological factors such as gastrointestinal enzyme, which regulates ph and intestinal transit rate, food, and disease, which often influence drug bioavailability from conventional dosage forms, can interfere with the accuracy of control release and removal of drug from the body. At some sites, the product that remains intact can be accommodated, which results in a slow release of the drug from the dosage form that results in a high localized concentration of drug from the system. As a sustained release formulation, drugs with a half-life of 1hr or less are difficult to formulate. The high rate of elimination of such drugs from the body requires a substantial maintenance dose of 8-12 hours per day. Since these products contain a large amount of opioids, they are not recommended for use in children.if the product is properly made and the entire drug contained there is released at one time or over a short period of time, it may be impossible to include a potent drug in such a scheme.

Tumor:

tumor is a benign or malignant growth of cells. A thick layer of tissue that arises when cells grow and divide more than they should or do not die when they should. Tumors are benign (not cancerous) or malignant (cancer). Benign tumors can grow large, but they do not spread to adjacent tissues or other areas of the body or invade them.

Types of tumor:

benign tumors are similar to a common skin wart, but they are not related to their original location, neither growing adjacent normal tissue nor spreading to other body parts.

Malignant tumors:

Malignant tumors are not limited to benign tissue but can invade surrounding normal tissue and spread throughout the body via the circulatory or lymphatic systems (metastasis). Only malignant tumors are properly classified as cancers, and it is their ability to invade and metastasize that makes it so dangerous. Although benign tumors can usually be surgically removed, malignant tumors spread to distant body sites, making them unable to be treated with such targeted therapy.

Tumor stages of tumor formation:

Cancer formation occurs when a single mutated cell starts to proliferate abnormally. Tumor formation is caused by additional mutations in the population, which are followed by selection for more rapidly growing cells. Studies of colon

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carcinomas have provided a clear example of tumor formation during the development of a common human disease. The first stage of tumor formation is characterized by increased proliferation of colon epithelial cells. One of the cells in this proliferative cell population is then thought to have a small benign neoplasm (an adenoma or polyp). As a result of further rounds of clonal selection, andenomas with increasing size and proliferative potential were cultivated. Malignant carcinomas are caused by benign adenomas, which are caused by the basal lamina penetration of the tumor cells into the surrounding connective tissue.

Several common drug delivery carriers are presented, characteristics, and application;

In recent years, many inorganic (non-metallic and metal) and organic materials (natural polymers, protein,dendrimer, etc.) have been studied as delivery carriers and developed into multifunctional drug delivery systems with the best size, shape, and surface properties to enhance the antitumor effect.

Non-metallic nps:

silicium and carbon are the most important non-metallic substances in close proximity to human life. Because of their intrinsic physical/chemical properties, low cost, and high biocompatibility, they can be used to make nanocarriers for cancer diagnosis and treatment. In recent years, non-metallic nps such as silicon nps, porous sinps (psinps), graphene, and graphene oxide (go) have emerged as a promising area for the development of drug delivery systems for cancer therapies. Sinps have a number of advantages in cancer care, including biocompatibility, biodegradability, low cytotoxicity, and genotoxicity, and they can be completely degraded by cells and tissues.

Metal NPs:

Metals are natural elements on the planet, as we all know, and their use is found in many fifield's, including agriculture, medicine, and our everyday life. In terms of nanomaterials, metals have also been used to make metal nps (mtnps). By mechanical attrition, laser ablation, photosynthesis, and chemical electrolysis by organisms such as viruses and plants, the most common materials used to synthesize mtnps are agnps, aunps, zno nps, fe2o3 nps, cuo nps, and al2o3 nps. Mtnps have not only their physicochemical properties, but also have antimicrobial, anticancer, catalysing, optical, electronic, and magnetic properties; they have been used in many industries including biology, food, agriculture, engineering, electronics, cosmetics, and medicine; and they have also been used in food and biomedical devices.

Natural Polymer NPs:

To make delivery carriers, glycan (chitosan) or protein (albumin and ferritin) have been used as natural molecular components. Chitosan (cs), a chitin derivative, is a natural biopolymer with biocompatibility, biodegradability, nontoxicity, antibacterial activity, wound healing ability, and anticancer properties. It has many uses as biomaterials for tissue engineering and wound healing, as carriers for drug, gene, and polypeptide delivery, among other things. However, its less solubility in water limits its usage. The functional groups of cs were modified by hydroxyl and amino groups to form cs derivatives such as carboxymethyl cs (cmc), which increased cs solubility by carboxymethylation as a hydrophilic modification that has many biomedical applications such as wound healing, bioimaging tissue engineering, and drug/gene delivery.

Liposomes:

Liposomes are cylindrical vesicles that carry both hydrophobic and hydrophilic drugs, with one or two concentric phospholipid bilayers separated by aqueous compartments, and have been extensively studied for many years. Liposomes have been used in the manufacture of anticancer drugs that do not cause unwanted toxic or antigenic reactions due to their biologically inert and biocompatible nature. Liposomes can be further modified with appropriate ligands (peptides, antigens, etc.). To create targeted liposomes and use overexpressed receptors as docking sites to deliver anticancer drugs, we use overexpressed receptors to form liposomes.

Exosomes:

Exosomes are extracellular vesicles created by mammalian cells. They are nanosized (50- to 100-nm) cup-shaped structures that are visible under the transmission electron microscope. On the surface of exosomes, there are many labelled proteins and ligand proteins, including alix, tetracaines (cd9, cd63, cd81), integrins, and cell adhesion

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molecules (cam), which represent their intracellular endosomal origin and attach to and deliver their payload to target cells. Exosomes have a long life, biocompatibility, low immunogenicity, and low toxicity in the environment, and they can be used to target disease tissues and/or organs based on their properties and origin with a specific cellular propensity.

Dendrimer:

Donald a tomalia made the first poly (amidoamine) (pamam) dendrimers (pamam) dendrimers in 1979 and first published his seminal work in 1985. Dendrimers are a relatively new class of synthetic dendritic polymers with three-dimensional, branched, highly monodispersed, stepwise synthetic macromolecular nanoscopic (1–100 nm) structure. Dendrimer architecture provides a novel way of solubilizing water-insoluble drugs and has three primary sites for drug entrapment, including void spaces (by molecular entrapment), branching points (by hydrogen bonding), and outside surface groups (by charge–charge interactions), resulting in a unique nanocontainer structure. It also provides a polyvalent platform to connect multiple biological targets, resulting in improved therapeutic outcomes, which have been used to produce a new nanodrug for antiviral and anti-inflammatory therapies. Dendrimers have been shown to increase transdermal permeation and specific drug targeting.

Targeting approaches/mechanisms for tumor therapy:

For tumor prevention, most common pharmaceutical drugs are usually administered by oral route or injection. However, drug molecules will be translocated slowly or rapidly into the bloodstream, resulting in a reduced bioavailability of the drug and more harmful side effects of the drug. To solve these problems, the functionalization of targeting moieties is a common method: proteins, nucleic acids, enzymes, receptors, and other functional biological molecules are commonly used to target action sites of drugs, and these molecules are usually located on the structural components or specific organelles. Therefore, a functioning ddss must be able to specifically deliver the drug to intended locations. We describe the potential target sites present in tumor cells or the tumor microenvironment in this section, as well as the corresponding targeting mechanisms; the tumor cell membrane, lysosome, endoplasmic reticulum, mitochondria, and nucleus are the most common biological locations for drug targeting.

Targeting the cytomembrane:

The cell membrane is a biological barrier that covers the cell surface and is mainly made up of membrane lipids and proteins. An intact cell membrane helps to maintain the cell's relative stability and thus promote normal life function. It also plays a vital role in many biological processes, including cell differentiation, signal transduction, as well as the exchange of substances and energy. The composition and structure of the cell membrane changes dramatically during cancelation of cells. According to studies, certain characteristics of tumor cells, such as invasion and migration, could also be related to abnormalities observed on the cell membrane. The specific antigens or receptors that are overexpressed on the tumor cytomembrane can be used as specific target sites for targeted tumor therapy. In a typical targeted drug delivery technique, the nanocarriers are then functionalized with the corresponding ligand or antibody to target over-expressed receptors or antigens on the cell surface. After nanocarriers are removed from the vessel, they can accumulate in tumor tissue and be internalized by a specific recognition mechanism between the receptor and the ligand (or antigen and antibody).

Lysosomal targeting:

Lysosomes are basically monolayer cystic particles that are formed in cells. They are a vital organelle. Hydrolase is present in lysosomes, of which more than 60 species have been identified so far, including proteolytic enzymes, nucleic acid hydrolase, lipase, glycosyl hydrolase, etc. Its primary function is to decompose intracellular macromolecules and proteins. When foreign substances enter the lysosome, they are decomposed by the hydrolase within. If the lysosome's membrane integrity is compromised, its abundant hydrolases will be released into the body, causing cell autolysis. According to studies, cationic substances and external stimuli (such as surfactants and heat, etc.) are linked to stress. Stress can play a role in life. Enzymes are released into the cytoplasm as a result of increased permeability of the lysosomal membrane, causing cell death. Therefore, therapies targeting the lysosomes have piqued a lot of interest in

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tumor therapy. Since the bulk of the nanoparticles will enter the lysosome after cell uptake, the precise targeting of lysosomes is relatively straightforward. Following the transformation of the surface ligand, the nanomaterials are endocytosed into primary endosomes, which are then fused with the lysosome. At this stage, the destabilizing agents embedded in nanoparticles, such as magnetic nano heaters, can quickly initiate the permeabilization of a variety of hydrolytic enzymes through the lysosomal membrane, resulting in complete cell apoptosis.

Targeting the endoplasmic reticulum:

The endoplasmic reticulum (er) is a closed-mesh piping system made up mainly of internal membranes. It is responsible for the synthesis, folding, and convection of nascent peptide chains. Er-misfolded protein is responsible for a variety of illnesses. The endoplasmic reticulum can also maintain homeostasis of intracellular calcium ions, which are important intracellular signalling molecules stored in the er. When exposed to external stimuli, the er will release calcium ions and induce caspase-8-related program apoptosis. Typical er stresses, such as protein misfolding and environmental stress (incubation with an anticancer drug), can induce a specific biological response of the er, which can result in cell death via the initial programmed apoptosis mechanism. This rule can be applied to a variety of cancer cells. The endoplasmic reticulum is therefore a potential tumor treatment target, but the current literature in this area is insufficient.

Targeting the mitochondria:

The mitochondrion is the primary site of aerobic respiration in cells. In addition to the role of a "power house," mitochondria also play a vital role in many regulatory processes including cell development and metabolism, apoptosis, calcium homeostasis, free radical generation, lipid metabolism, and so on. Mitochondria can control programmed cell death by controlling the membrane potential. However, mitochondria in most tumor cells are in a constant state of dysfunction, with poor membrane permeability and abnormal release of apoptotic signals. Mitochondria are potential targets for tumor treatment. Mitochondria have a highly negative membrane potential that is derived from their position in the body. Mitochondrias provide atp energy to support various biological functions. They are constantly pumping out protons (h+, na+, etc.) From the intima. In addition, cancer cells' proliferation rate is higher than that of normal cells, so cancer cells need more energy to support their growth. The membrane potential of mitochondria in tumor cells is therefore lower than that of normal cells. Based on this characteristic, mitochondria-targeted therapy could be developed.

Targeting the cell nucleus:

The cell nucleus is the building block of a cell and plays a vital role in cell metabolism, growth, and differentiation. It is the primary storage site for genetic material. The nucleus is where the action sites of most therapeutic anticancer drugs, such as dna intercalators and topoisomerase inhibitors, are located. Thus, targeting drugs directly to the nucleus will effectively raise the therapeutic effect due to the bypassing of drug efflux pumps, making nuclei-targeting a vital delivery technique for tumor therapy.

Targeting the tumor microenvironment:

The tumor microenvironment is closely related to the pathological condition of tumors. It is involved in tumor formation, growth, expansion, and metastasis. In the field of tumor-targeted dds, tumor microenvironment sensitivity has also been closely investigated, taking advantage of the numerous similarities between tumor microenvironments and normal tissues, such as ph value, vascular abnormalities, and ecm structure.

TDDSs for tumor therapy:

The term "targeting" refers to the ability of nanocarriers to safely reach pharmacological sites in a highly selective manner in the tdds. A well-trained drug nanocarrier facilitates the targeted delivery of chemotherapeutics to tumor sites but not to healthy tissues, particularly those that contain hydrophobic antitumor agents. This could allow for the maximum therapeutic benefit with no adverse side effects. In general, there are two main categories of targeted delivery: passive targeting and active targeting. As shown by the following diagrams, the physical properties of nanocarriers are closely related to targeting effectiveness. Nanocarriers of appropriate size, for example, were much

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more effective at facilitating the transport and accumulation of nanocarriers in tumor sites. As for active targeting, the fabricated nanocarrier could actively interact with the target cells and deliver the cargo to the desired location. Active targeting is based on the specific relationship between targeting moieties embedded on the surface of nanocarriers and the receptors embedded on the surface of diseased tissues/cells. The two targeting strategies' unique strengths are discussed in the next section.

Passively targeting DDS:

Most solid tumors have unique pathophysiologic features that are not present in normal tissues or organs, such as extensive angiogenesis, vascular abnormalities, a dysfunctional lymphatic drainage/recovery system, and a significant rise in the production of a variety of permeability mediators. Therefore, the passive targeting of solid tumors is largely dependent on the observed enhanced permeation and retention (epr) effect in solid tumors.

Physiological factors affecting the EPR effects:

On a daily basis, the effect of the epr on tumors has been used to produce anticancer drugs. Despite its specificity, it is also highly affected by the state and the form of tumors. In addition, tumor vessel shape and pore size will vary dramatically within the same tumor or between different tumor types. The epr effect in tumors is influenced by many factors, of which the most prominent are listed below.tumor tumor growth environment, for example, the shape of the vascular bed and surrounding stroma vascular factors, as well as specific inhibitors are used in the body that can reduce blood pressure. Co-medications and their effect on stroma and blood pressure (increased tumor blood flow due to intratumorally hypertension).

Nanomaterial factors improving the EPR effect:

Nanocarriers of the right size and shape are usually modified with various functional molecules/motifs, such as polyethylene glycol (peg), in an excellent tddss based on passive targeting. According to a variety of studies, nanoparticles' circulation stability and targeting ability are largely attributed to their shape, shape, and surface characteristics. Nanocarriers have a variety of physicochemical properties, including elasticity.

Size and shapes:

The epr effect, according to the above discussion, would be greatly affected by the size of nanocarriers/macromolecular drugs due to the high interstitial fluid pressure and the poor lymphatic drainage in the tumor microenvironment. The long-circulating nanocarriers with a suitable size (around 100 nm) are prone to accumulation in the tumor. The purpose of using nanoparticles with a size of about 100 nm for drug delivery is to be much smaller than 400 nm, allowing their effective escape from the deficient tumor vessels. their size should be less than 10 nm to prevent kidney filtration. their size should be less than 100 nm to prevent capture by the reticuloendothelial system and liver.

Surface charge:

The surface charges of the nanocarriers can have a major effect on phagocytosis and their blood circulation. Negatively charged or neutral nanoparticles have a random effect on np blood clearance, but positively charged nanoparticles are generally accepted to have a negative effect on their in vivo stability after plasma exposure, as shown by the study. Positively charged nanoparticles are internalized by cells faster than neutral or negatively charged nanoparticles.

Surface wettability:

Surface hydrophobicity is another important factor in epr-dependent drug delivery, in addition to particle size, shape, and charge status. In general, hydrophobic nanoparticles are more likely to be coated with specific proteins such as immunoglobulin and plasma proteins.

Advanced drug delivery system based on passive targeting:

Many novel ddss have been developed from nanoparticles of the right size, shape, and surface properties that were commonly used in conjunction with multiple functional motifs to cooperatively regulate the multi-stimuli-responsive

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functions of tddss and enhance the epr effect, increasing the accumulation of nanocarriers in tumor sites and facilitating localized cargo delivery. In this section, we will mainly concentrate on those advanced tddss that are based on passive targeting.

Actively targeting DDS:

Active targeting. Active targeting, also known as ligand-mediated targeting, involves attaching specific ligands/antibodies to the nanocarriers. This approach was theoretically based on the paired ligand–receptor or antigen–antibody recognition on tumor cell surfaces, and it can increase tumor uptake and tumor penetration, as well as increase the therapeutic effectiveness of the anticancer drugs. Since the tdds is designed to bind to a receptor that is overexpressed on tumors (including tumor cells and tumor vasculature), but not expressed by normal cells, it may also reduce undesirable side effects (fig. 2). 1) in addition, the flexible tdds can effectively deliver antitumor drugs to the cytoplasm in response to a variety of endogenous (ph, redox, hypoxia, etc.) conditions. Toxic substances (ph, redox, etc.) are present in the body. And exogenous (light, ultrasound, magnetic, etc.). Following tumor cell internalization, there were stimuli that significantly increased the antitumor effectiveness. Active targeting has attracted increasing attention and is well integrated into ddss, and these actively targeting ddss have achieved an averagely higher success than non-targeted ddss, such as increased cytotoxicity to tumor cells and the reduction of side effects, as shown by the following section. In the following section, we will discuss the most commonly used active targeting ligands in the most common advanced active targeting-based ddss.

Targeting ligands:

Cytomembrane targeting:

The asialoglycoprotein receptor (asgpr) is an overexpressed receptor on the surface of the tumor cell membrane that can specifically bind to several sugar ligands (e.g., galactose, lactobionic acid) with high affinity; however, its expression on normal cells/tissues is almost negligible. It could also be used as a promising active site for dds conjugated with targeting ligands. We also developed a la-col-linker-msn nano reservoir made up of collagen-capped mesoporous silica nanoparticles for tumor treatment. Collagen was grafted onto the msn surface, and disulphide connections prevented the mesopore channel from leaking. The tdds, which have a high biocompatibility, had a higher cell-specific targeting efficiency and a redox-responsive drug release profile in vitro. In the following experiments, we described the tumor cell-specific endocytosis pathway of la-targeted msn-based tdds, which was specifically internalized by tumor cells by asgpr-mediated endocytosis. We then made redox-responsive and enzyme-responsive tddss based on la-targeted msn/hmsn (hollow mesoporous silica nanoparticles) and further investigated the antitumor effect in vivo. The la-functionalized nanocarriers enhanced the selective delivery/accumulatio of nanocarriers to tumor tissues, which could then locally release the antitumor drug when there is a high concentration of gsh or matrix metalloproteinases, causing cell death.

Lysosome targeting:

Lysosomes are a promising therapeutic option for the initiation of apoptosis in cancer cells due to lmp-induced leakage of hydrolytic enzymes, particularly the cathepsins, into the cytoplasm. Domenech and his coworkers devised a protocol that could be used to induce lysosomal death. In this study, the epidermal growth factor (egf) ligand was grafted onto iron oxide magnetic nanoparticles (mnps), after which the functionalized mnps are converted into endosomes and lysosomes by egf receptor-mediated cell internalization. The lysosomal membrane lmp was created by an alternating magnetic field.

Targeting of the endoplasmic reticulum:

The endoplasmic reticulum stress response can lead to the onset of the cell apoptotic response. Therefore, targeted delivery of drugs to tumor cells' endoplasmic reticulum can increase the effectiveness of an anti-cancer drug. Zou and coworkers described luminescent platinum (ii) complexes containing bidentate n-heterocyclic carbine (nhc) ligands. After cell internalization, (nhc) ligands are able to guide complexes specifically to the er, triggering apoptosis in two

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directions. The formation of mitochondrial damage, which is a sign of early apoptosis, is one of the factors. Another example is the upregulation of related genes to induce er stress and then the onset of the apoptotic process.

Mitochondria targeting:

A lipophilic tpp can effectively attach to mitochondria due to its higher mitochondrial membrane ability. By coating with tpp., jung and co-workers made mitochondria-targeting iron oxide nps (io np). Since tpp has a greater affinity with the mitochondria, tpp-io np was gathered more in the mitochondria; mitochondria-targeted hyperthermia therapy demonstrated a promising anticancer treatment effect.

Targeting of nuclei:

A nuclear localization signal (nls) could quickly combine nuclear pore complexes (npcs) and mediate cargo into the nucleus. Tat, a common nls peptide, was used to target the nucleus. Pan and coworkers developed a special nuclear-targeted dds of 30 nm to effectively address mdr. In this study, uniform and monodispersed msns and tat-functionalized msns (msns–tat) were synthesized. Msns–tat were mainly present in the nucleoplasm and the perinuclear region of mcf-7/adr cells, while msns were present in the cytoplasm only, which is due to the tat peptide's unique function. Dox-msns–tat, on the other hand, increased cytotoxicity in mdr cancer cells (mcf-7/adr), indicating that direct release of the anticancer drug into the nucleus can effectively prevent p-gap-mediated drug delivery.

Tumor micro environment sensitive targeting.

Since direct tumor microenvironment targeting (typically tumor vasculature targeting) not only overcomes the diffusion barrier of the dds across the tumor, but also inhibits tumor development and metastasis by destroying the vasculature, the tumor microenvironment-sensitive tddss have emerged to be a very important branch of tumor targeting. Chang et al., 2002. For mouse and six types of human solid tumors, ivo peptide-targeted liposomal ddss have been developed, specifically targeting both tumor vessels in tumor xenografts. It significantly increased the therapeutic effectiveness, decreased tumor angiogenesis, and stopped tumor formation. In addition, the low ph environment of tumoral ecm was also a potential target for tumor therapy. For targeted tumor therapy, lo andro-workers developed a tumor-ecm, ph-induced liposome (ecm-targeting liposomes). The fabricated tdds showed a significant higher antitumor activity and lower toxicity in vivo.

III. PRECLINICAL STUDIES OF TDDSS

Preclinical studies of passively targeting DDSs

These nanocarriers can deliver various antitumor agents, including sirna, cpt, ptx, and sn38, to tumor sites with high antitumor activity. The fda approved doxils as the first nanocarrier for clinical use in 1995. It was used to treat ovarian, breast, and other cancer conditions. The dox-loaded liposomal nanocarrier was combined with peg to prolong the dox-loaded liposomal nanocarrier's half-life. to increase the tumor site dox content, the dox-loaded liposomal nanocarrier was combined with peg. It was enriched in tumors as a result of the epr effect. Doxils can significantly reduce the chance of dox-induced cardiotoxicity and extend its elimination half-life from 0.2 to 55 hours.59 the new anticancer nonpharmaceutical from nektar therapeutics uses a multi-armed peg polymer as the carrier layer for irinotecan delivery. The irinotecan molecules are covalently attached to a four-armed peg. In the preclinical studies, nktr-102 plasma had a long pharmacokinetic life with a half-life of 15 days, compared to 4 hours with free irinotecan.

Preclinical studies of actively targeting DDSs:

As previously discussed in previous sections, actively targeting ddss could increase the selective uptake and accumulation of drug-loaded nanocarriers in tumor tissues, reducing side effects. Several potent tddss that are functionalized with active targeting ligands have been developed and tested in clinical trials. In clinical trials, several ddss are currently being investigated in table 3.bind-014 is the first targeted polymeric nanoparticle. Docetaxel was encapsulated in biodegradable plga–peg nanoparticles and conjugated to prostate-specific membrane antigen (psma). Through receptor-mediated endocytosis, bind-041 demonstrated improved circulation stability and more effective

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tumor-specific drug accumulation (more than 10-fold higher than free docetaxel). To achieve the same tumor-inhibiting effect, only one-fifth of the original medication dose is required

IV. THE IDEAL FEATURES OF A TARGETED DRUG DELIVERY SYSTEM

1 The product should be stable, effective (non-toxic), compatible with body fluid and biodegradable.
2 The drug should be delivered only to the intended destination.
3 At a predetermined rate, monitor the drug release
4 The rate of drug delivery is not affecting the pharmacological effect.
5 During transportation to the intended location, the drug should have a minimum leak.
6 The drug delivery procedure should be simple, quick, and cost-effective.

V. ADVANTAGES AND DISADVANTAGES OF TDDS

Advantages:

1 By targeting a specific location, the drug's toxicity is reduced.
2 With a small dose, the desired drug response can be achieved.
3 Avoid the first-pass effect.
4 Improvement in the drug absorption from the intended location
5 drug targeting resulted in no peak and valley plasma concentrations.

Disadvantages:

1 High dose levels result in rapid drug removal from the body.
2 The immune response may be triggered by the device's originator.
3 The drug delivery system is not localized in the tumor tissue for long enough to occur.
4 The dissemination and redistribution of commercially available drugs.
5 The development, storage, and administration of the intended drug delivery system require a great deal of expertise in this area.

VI. CONCLUSION

Nanomedicine, particularly nanoscale ddss, has the ability to deliver drugs to cancer sites by using nanocarriers. As compared to conventional chemotherapy drugs, nanoparticle-based ddss can deliver therapeutic drugs to tumor sites with high specificity, limiting the therapeutic drug's non-targeted tissue uptake and, in turn, reducing side effects. For a successful dds, nanocarriers with the right size and surface properties will effectively enhance the pharmacokinetics and biodistribution of the therapeutic drugs, but the targeting capability is crucial to both increasing the therapeutic effectiveness and attenuating the side effects. The two most popular targeting techniques are passive targeting and active targeting. The term passive targeting is most commonly used. Passively targeting ddss can invade from the blood vessels and then persist in tumor sites due to a weakened tumor vasculature structure and deteriorating lymphatic drainage in tumor tissues. The targeting efficiency is closely related to the degree of tumor vascularization/angiogenesis and the physical properties of nanocarriers. The actively targeting dds are mainly delivered to tumor sites via the epr effect, followed by a highly efficient cell uptake process that relies on a unique molecular recognition mechanism between the targeting ligands conjugated on the surface of nanocarriers and the overexpressed receptors/antigens on the surface of target tissues/cells. All passive and active targeting strategies have their drawbacks and are being scrutinized in preclinical/clinical studies. These tddss are often combined with specific functionalized ligands such as targeting agents, peg analogues, cell-penetrating peptides, etc., resulting in a long circulation time, reduced res effect, high uptake efficiency, controlled drug delivery, and reduced side effects.

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IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023

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