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EMERGING TRENDS OF DRUG TARGETING IN TUMOR THERAPY

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ABSTRACT

Cancer is the second cause of death in many countries. Because of the increased threat of cancer, new and advanced approaches have been developed and evaluated for cancer therapy. To lower cytotoxicity, and to enhance therapeutic effects, targeted drug delivery systems for anti-tumor drugs were explored. The drug delivery system includes polymeric carriers and colloidal carriers like liposomes, microspheres, antibodies that directed against antigenic receptors present or expressed on tumor cells and carry drugs that interfere with tumor growth. There are different approaches for tumor targeting like passive targeting, active targeting, trigger drug delivery etc. This review discussed the various emerging trends of drug targeting for tumor therapy.

Keywords: Active targeting, Drug delivery, Nanoparticles, Passive targeting, Tumors, Trigger delivery.

INTRODUCTION

Tumor is an abnormal growth of cells and tissue that may be solid or fluid-filled. Tumor is also known as a neoplasm. Tumor starts when the healthy cells of DNA are damaged, forming the cells out of control. In general, tumors are categorized into three groups.

BENIGN: These are not cancerous, even they cannot spread. Benign tumor will persist in its current form. Once it is removed this tumor does not return. They are often nearby a safeguarding "sac" immune system performs a mechanism that segregates it from the rest of body and enables it to be removed easily. Benign is capsulated, non-invasive, slow-growing [1].

Examples: Fibroma, adenoma, emangioma, eningioma, ipoma.

PREMALIGNANT: It is not deal with a premalignant tumor. Even it is not a cancerous but become visible to be acquiring the properties of cancer. A premalignant is also called precancerous. A lesion or new mole on the skin refers to a precancerous growth that is not cancer but could develop into cancer. Many times, cases of melanoma, carcinoma, basal cell, and squamous cell carcinoma begin as precancerous growths [2].

MALIGNANT: Malignant tumors are cancerous. They can grow spread and get worse. Cancer cells invade surrounding tissues, enter blood vessels and metastasize to different sites. They may not have symptoms initially and the first indication may be the detection of a painless lump [3]. These are cancerous fast-growing, non-capsulated, metastasized, invasive and infiltrated.

PHYSIOLOGY OF TUMOR:

Tumor arises from:

Agents that damage genes: regulating the cell proliferation and that promote the tumor cell migration.

Agents that do not damage genes: selectively enhance the growth of tumor cell or their precursors.

Cancer:

- The word cancer is derived, from the Latin word crab. The cancers are often very irregularly shaped like a crab, they grab on and don't let go. The cancer term confer to a new growth that can invade surrounding tissues, metastasize (spread to other organs) and if untreated that may eventually lead to the patient's death [4].
- A tumor becomes cancerous when cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors. Tumors can grow and interfere with the digestive, nervous, and circulatory systems and they can release hormones that alter body function [5]. Tumors that stay in one spot and demonstrate generally limited growth are recommended to be benign.
- Cancerous cells can migrate throughout the body using blood or lymph systems thereby destroying the healthy tissue. Those cells manage to divide and grow, making new blood vessels to feed themselves, a process called angiogenesis.
- Mutations are the most common cause of cancer. Every mutation can alter the behaviour of the cell somewhat genes that regulate cell growth and differentiation must causes genetic and epigenetic changes at many levels [6].

TUMOR VASCULATURE VS NORMAL VASCULATURE:

- The tumor vasculature was different from the normal vasculature in the following respects.
- Tumor vessels are larger than that of normal vessels presumably is due to the large pores in the vessel wall. This could be accounted for by the options of the basement membrane adjacent to endothelial cells [7].
- Tumor vasculature endothelium shows the retarded and altered expression.
- Turnover time of normal endothelial cells is estimated in the range of a thousand days or more, whereas tumor endothelial cells grow with a turnover time of only four to five days.
- Heterogeneity in angiogenic peptide expression results in a heterogenic endothelial cell population [8].

TUMOR DEVELOPMENT:

The tumors arise from the effects of two different kinds of carcinogens. One of the categories comprises agents that damage genes involved in controlling cell proliferation and migration. Cell adhesions is a prerequisite for cell survival in the normal condition and occur in the anchoring of cells within or with an extracellular matrix and allow cells to survive and proliferate. The mutation allows the cell to develop with additional alterations and accumulate increasingly large numbers, forming a tumor that consists mostly of the abnormal cell [9]. Another category includes that agents do not damage genes but instead selectively enhance the growth of tumor cells. The primary danger of malignancies is that they can metastasize allowing some of their cells to migrate and carry diseases to other parts of the body. Finally, illness can reach the disruptive one of the body's vital organs. Epithelial tumors are the most common malignancies. The tumors mass emerges as a result of mutations in genes and genetically altered cells.

MECHANISM AND STAGES OF TUMOR DEVELOPMENT:

Several stages of tumor development can be explained by different researchers.

Different stages are:

I. The tumor evaluation commences when a cell within a normal population sustains a genetic mutation that expands its tendency to proliferate when it would normally rest.

II. Genetically altered cells and their offspring continue to appear normal but they reproduce excessively and lead to a condition known as hyperplasia. After sometimes months or years's one in a million of the cell. Cells sustain additional mutation with loss of control on cell growth [10].

III. The offspring of the cell not only divide excessively but also exhibit abnormality in shape and orientation. The tissue is now said to exhibit a condition known as dysplasia. After some time a further mutation alters the cell behaviour.

IV. The genetically altered cells become more abnormal in growth and appearance if the tumor mass does not invade through any boundaries between tissues, it is known as an in-situ tumor. This tumor may stay contained indefinitely or some cells may acquire additional mutations.

V. A malignant tumor results if the genetic changes allow tumor mass to initiate an invasion of underlying tissue and to cast off cells into the blood or lymph. The defector cells may install new tumors throughout the body [11].

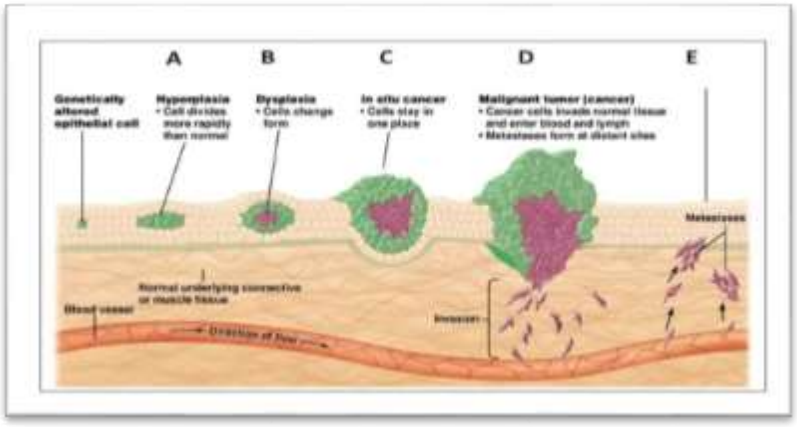

Fig.1. Stages of tumor development

DRUG DELIVERY SYSTEMS FOR TUMOR:

- Microspheres are the preferable drug delivery system for tumor therapy. Anti-tumor drugs formulated in microspheres suitable for subcutaneous injection, nanoparticles for delivery of antitumor drugs, magnetic targeted microparticle technology, antitumor drugs bound to carbon particles, nano-erythosomes, albumin-based drug carriers are the most suitable drug delivery system.
- Another drug delivery system of tumors is liposomes. Liposome plays a significant role to formulate antitumor drugs with different approaches to target the tumor cells. [12].
- Next, monoclonal antibodies bi-specific antibody fusion protein, drug and radio immunoconjugates, immunotoxins, combined use of maps and cytokines, two-step targeting using a bispecific antibody, single-chain antibody-binding protein technology.
- Antineoplastic drug implants into tumors, PEG technology, pressure-induced filtration of drugs across vessels to tumor and vitamins also used as a carrier for antitumor agents. Delivery across the blood-brain barrier, chemotherapeutic agents incorporated in biodegradable polymer wafers, boron neutron capture therapy, iontophoretic delivery into subcutaneous tumors.
- Targeting antitumor drugs to tumor blood vessels, peptides targeted against integrin cell adhesion proteins, drugs to induce clotting in tumor vessels, vascular targeting agents, etc.[13]

TARGETED DRUG DELIVERY:

A drug is delivered at a specific site in the body where it has the remarkable effect, instead of allowing it to diffuse to various sites, where it may cause damage or trigger side effects.

Here specific interactions occur between a drug and its receptor at the molecular level [14].

Effective targeted drug delivery systems require four key requirements and they are:

1. Retain 2. Evade 3. Target 4. Release

These four key requirements lead to an effective drug in the tumor targeting drug delivery system.

- Modified with targeting moieties, like antibodies, small peptides, specific molecules, antibody fragments etc. The carriers (nanoparticles) can target specific receptors and antigens expressed on the tumor cell surface or the tumor microenvironment, reducing side effects on normal cells [15].

- Various vitamins and nutrients are essential for quickly growing tumors. For that reason tumor cells over express many tumor specific receptors that can be considered as targets to carry out cytotoxic agents into a tumor.
- At the site of action, preferably localizing its pharmacological activities.
- To show therapeutic response because it brings off cellular concentration.
- Very often a variety of homing devices are being employed to direct the therapeutic agent and carriers to the particular site [16].
- Mechanistically, these homing devices are the special molecular signatures that are expressed to a greater extent at the tumor tissues such as folic acid etc.
- The tumor targeting is required due to limited accessibility of drugs to tumor tissues, the requirement of high doses, intolerable cytotoxicity development of drug resistance and non-specific targeting [17].
- Targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with specific targets that are needed for carcinogenesis and tumor growth.
- Targeted delivery refers to predominant drug accumulation within a target zone that is independent of the method and route of drug administration [18].

VARIOUS APPROACHES FOR TUMOR TARGETING:

i. Passive targeting:

- Passive targeting is based on drug accumulation in the areas around the tumors with leaky vasculature; commonly referred to as the enhanced permeation and retention effect.
- Passive targeting explains the anatomical differences between normal tissue and tumor tissue to deliver the drugs [19].
- Drugs administered passively in the form of product or inactive form, when reaches to tumor tissue, becomes highly active.
- Nanoparticles will follow the biological mechanisms known as ERS (enhanced retention system).
- Size should be below 100 nanometers in diameter and the drug accumulates around the tumor.
- Passive targeting involves the transport of nanocarriers through leaky tumor capillary fenestrations into the tumor interstitium and cells by convection or passive diffusion and selective accumulation of nano-carriers and drug then occurs by EPR effect [20].

Macromolecular conjugates:

Polymer drug conjugate

Protein drug conjugate

Antibody-drug conjugate

Particulate systems:

Liposomes

PEGylated liposomes

Polymeric micelles.

ENHANCED PERMEABILITY AND RETENTION EFFECT:

- The enhanced permeability and retention effect is a unique phenomenon of solid tumors based on their anatomical and patho-physiological differences from normal tissues.
- Macromolecular drugs could accumulate and retain in solid tumor tissues selectively but they will not distribute much in normal tissues [21].
- EPR based chemotherapy is thus becoming an important strategy to improve the delivery of therapeutic agents to tumors for anticancer development.
- Classically, the cell proliferation leads to the formation of solid mass and upon reaching a specific size cells in the interior starts getting deprived of the nutrients release of growth mediators signaling the development of blood vessels within a tumor [22].
- Within the size of 20-2000 nm, the absence of basal membrane leads to fenestrations. And Assembled blood vessels are generally leaky owing to the absence of basal membrane.
- The principal factors affecting EPR includes vessel architecture, interstitial fluid composition, extracellular matrix composition phagocyte infiltration, presence of necrotic domains, factors about the colloidal carriers such as blood circulation time, particle size, particle shape, surface charge, and surface fictionalization if any (eg; stealth characterization by pegylation) [23].
- The presence of fenestrations results in poor resistance to the extravasations of macromolecules to the tumor microenvironment and contributes to the enhanced permeation part of EPR.
- Simultaneously, it has also been found that tumor mass is associated with non-uniform lymphatic drainage and experience huge physical stress owing to rapid growth in the dimensions of the tumor mass this leads to the severe compromise in the drainage functionality of the vessels and contributes to the retention part of EPR effect [24].

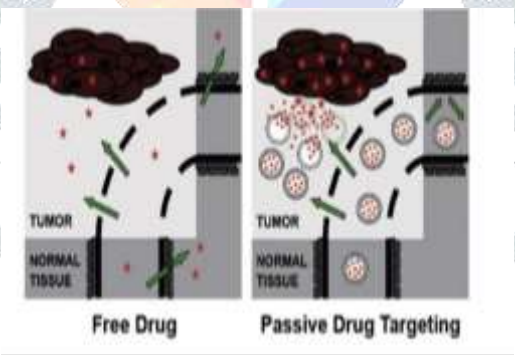

Fig. 2. Passive drug targeting

ii. Active targeting:

- Based on some specific ligand-receptor interactions, Active targeting is used to narrate specific interactions between drug/drug carriers and the target cells.
- Active targeting means a particular ligand-receptor type interaction for intracellular localization which occurs only when extravasation and after blood circulation [25].
- Active drug targeting is generally implemented to improve target cell recognition and target cell uptake, and not to improve overall tumor accumulation.
- For several reasons, there is no actively targeted liposomes, polymers, micelles etc. Approved for clinical use and very few used in clinical trials. In clinical trials, formulations are improving cellular uptake for therapeutic efficacy [26].

- In this prototypic example, it is a transferrin receptor-targeted cyclodextrin based polymeric nanoparticle containing siRNA, they are unable to enter cells and which they are needed to be delivered into the cytoplasm of tumor cells to exert an antitumor effect [27].

Components of active targeting:

a. Drug b.Ligand c.Carrier

Ligand mediated targeting is the major approach that involves ligands developed against cell receptors or antigenic determinants expressed on tumor cells or vasculature [28].

EXAMPLE: Transferrin, Ectins, Galactosamine, Folate.

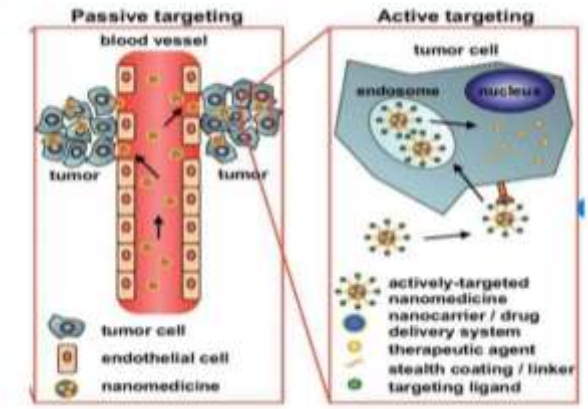

Fig. 3. Mechanism of passive and active targeting

iii . Triggered drug delivery:

- In the triggered drug delivery, the tumor microenvironment differs from the normal cells microenvironment.
- The advantage of the different pH, temperature and presence of enzymes is used to release the drug in the tumor microenvironment.

1. pH-sensitive drug release.

2. Enzyme activated conjugates.

3. External stimuli triggered (magnetic field)

- The triggered release nano-drug release system emerges as a promising cancer therapeutic modality to solve the critical issues of traditional chemotherapy. These strategies aim to integrate anti-cancer drugs with nanocarriers to form host-guest drug delivery systems [29].
- In the triggered delivery system they are triggered to release their contents upon exposure to external stimuli, such as light, heat, ultrasound and magnetic fields [30].
- In case any problems occur in the triggered release of drug delivery overcome these problems many different efforts are currently being taken in industries and academic level.
- Here not only improve the stimuli response of tumor targeted nano-medicines but also develop external stimuli more effective and more selectivity to the targeted tissue.

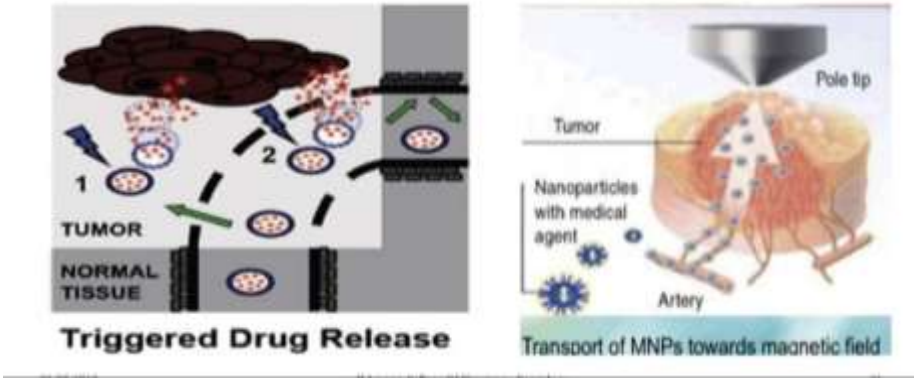

Fig. 4. Mechanism of triggered drug delivery

NANOCARRIERS AS DRUG DELIVERY SYSTEM:

- In the diagnosis/treatment of cancer, different drug delivery systems are used mainly to target the diseased cells without affecting the normal cells [31].
- For the Delivery of the drugs to site-specific targets, Nanocarriers are very helpful in the drug delivery process and also useful to allow the drugs to be delivered in certain cells and organs but not in other places in the body.
- A site specifically is a major therapeutic benefit since it prevents drugs from being delivered to the wrong places [32].
- The transport barriers of nanoparticle delivery to tumors.
- Systemically administered anti-tumor nanoparticles have to travel through the tumor vascular network, cross the vessel walls, penetrate in the interstitial space, and reach target cells effectively.
- Nanoparticles of 1000 nm drug carriers have processing mainly advantage of non toxicity, prolonged circulation, biodegradability and biocompatibility [33].
- Nanoparticles mainly follow mechanisms such as an enhanced retention system.
- In the normal tissue region, the nanoparticles are retained in the bloodstream.
- In the tumor tissue region, nanoparticles accumulate through leaky vasculature.

TARGETED THERAPIES AVAILABLE IN TUMOR TREATMENT:

To use in cancer treatment many different targeted therapies have been approved.

They are:

- Hormone therapies
- Signal transduction inhibitors
- Toxin delivery molecules
- Gene expression modulator
- Apoptosis inducer
- Angiogenesis inducer
- Immunotherapy

TARGETED MOLECULAR THERAPY:

The drug targeting concept was thought to be redefined has been severely invalidated in case of some pathological manifestations. In this molecular therapy molecular targets on the surface membrane of malignant

cells and here targeted using the counter ligand or specially designed antibodies. Altered expression of cell adhesion molecules and their ligands [34]. Altered expression of certain growth factors and some receptors. It is one type of personalized medical therapy designed to treat cancer, by interrupting unique molecular abnormalities that drive cancer. Targeted therapies are drugs that are designed to interfere with a specific biochemical pathway that is central to the development, growth and spread of that particular cancer [35].

TREATMENT WITH IMMUNOTHERAPY:

Immunotherapy of tumors there means the main aim to attack diseases with defense mechanism to the body, has been recognized widely and effective involvement of various immune components of the body.

The components are antigens (vaccine) antibodies, monoclonal antibodies, cytokines and immunotoxins etc. These are all considered as possible strategies in tumor therapeutics [36].

Immunotherapy treatment for tumors is designed to repair, stimulate or enhance the immune system's response using the patient's immune system to fight cancer.

Target specific cancer cells, thereby potentially avoiding damage to normal cells. Recognizing and destroying, cancer cells make it easier for the immune system. Prevent or slow tumor growth and spread of cancer cells [37].

Example: Vaccine therapy.

TREATMENT WITH GENE THERAPY:

Cancer is caused by changes in our genes. To modify cancer cells at the molecular level and replace a bad gene with a healthy one, gene therapy is designed. Then new gene is delivered to the target cell via a vector which is usually an inactive virus or liposome tiny fat bubble. Several gene therapy strategies are included in gene therapy.

1. Modify the function of oncogenes and tumor suppressor genes [38].

2. Modification of the host immune response towards the tumor.

3. Disruption of tumor neovascularization.

4. Lysis of tumor cells with replication-competent viruses.

5. Finally suicide gene therapy where inactive prodrug converted into a cytotoxic drug by gene expresses enzymes [39].

ANTIBODY DIRECTED ENZYME PRODRUG THERAPY:

i. First injection: The monoclonal antibody is given with the enzyme attached, through injection.

ii. Second injection: In the second step as a drug the prodrug is given [40].

iii. Activation: The prodrug comes into contact with an enzyme drug then able to destroy the cancer cells.

iv. Selectivity: enzyme antibody conjugate does not attach to normal cells and the drug does not affect them [41].

LIMITATIONS OF TUMOR TARGETING:

In the treatment of cancer, drug targeting is indispensable in the selective and quantitative accumulation of the drug in the target organ or tissue.

Cancer cells become resistant to the resistance can occur in two ways-

1. The targeted therapy no longer interacts well with it because the target itself changes through mutation.

2. The tumor finds a new pathway to achieve tumor growth that does not depend on the target.

SIDE EFFECTS:

- The most common adverse effects noticed in targeted therapies are;
- Liver problems and diarrhea, like elevated liver enzymes and hepatitis.
- Skin problems such as rashes, dry skin, nail changes, hair depigmentation.
- And also Problems with wound healing and blood clotting.
- High blood pressure.

CONCLUSION:

In drug targeting tumors, from the last few years many different systems and strategies have been developed and investigated. Tumor targeting can be achieved through passive and active targeting approaches. Several systems have been demonstrated excellent tumor targeting properties such as macromolecular conjugates, liposomes, polymeric micelles. Anticancer drugs with different physicochemical properties are delivered by these drug delivery systems and several targeting ligands were successfully incorporated to enhance tumor specific targeting. An optimal tumor targeted delivery system shall be realized shortly.

FUTURE PERSPECTIVES

For cancer therapies, the ideal targeted drug delivery systems deliver the drug only to the target tumor. As tumors may not be eradicated by just aiming at one target, it may also be necessary to simultaneously aim at multiple targets. Thus, it might be worthwhile to develop a magic shotgun. Strategies that deliver multiple drugs and deliver the drug to multiple targets.

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CONFLICT OF INTEREST

There is no conflict of interest among the authors.

AUTHORS CONTRIBUTION

All the authors contributed equally to this manuscript.

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