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Drug Targeting In Neoplastic Disorders

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ABSTRACT

The review on drug targeting in neoplastic disorders emphasizes the various targeting techniques for effective treatment of the condition. Neoplasm refers to the new growth and its common in any individual, uncontrolled neoplasm results in condition called neoplastic disorder or tumor or cancer. Globally 14.1 million cancer cases were reported in 2012 and the number is expected to reach 24 million by 2035. This review outlines the advances in drug targeting to the neoplastic disorders keeping in view on the highlights the novel drug delivery systems like liposomes and particulate system like nanoparticles problems associated with conventional chemotherapy and radiation therapy. It usage in treatment of cancer and effective targeting ways to target the tumor cells without affecting the normal cells.

Keywords: Chemotherapy, Liposomes, Nanoparticles, Neoplasm.

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INTRODUCTION

As the evolution of science is advancing the advancement of diseases are also progressing. Worldwide cancer figures as one of the major cause of the morbidity and mortality according to World Health Organization1. Globally 14.1 million cancer cases were diagnosed in 2012 and the number is estimated to reach 24 million by 20352. Around 8 million deaths were reported in 20121. Neoplasm refers to the new growth of cells which is a common mechanism involved in the anabolic processes and for the survival of living organisms. Growth among the cells is primarily regulated by two genes i.e. oncogenes and tumor suppressor genes. Any loss in the regulatory mechanism of these genes will result in uncontrolled neoplasm which is commonly referred as neoplastic disorder or cancer or tumor. Cancer may be formed in any part of the body and it is mostly observed in lungs, breast and prostate according to World Cancer[1]

CELLULAR GROWTH-CANCER FORMATION

Cellular growth is an intrinsic mechanism for multiplication of cells and it is majorly regulated by two important classes of Gene's. They are oncogene and tumor suppressor genes. Oncogenes or proto-oncogenes also help in the promotion of cellular growth by coding of growth stimulatory protein whereas tumor suppressor genes are useful to inhibit the growth of the cells. Prior to cell proliferation the cell enlarges and divides and for the survival of a cell it is needed to get attached among them or to the extra cellular matrix, cell adheres to the extracellular matrix with the aid of area codes. If cell adhesion does not takes place cell may undergo apoptosis which results in death of cell. Any of the mutation in either of the genes results in excessive multiplication of the cells which is a neoplastic disorder or commonly called as cancer. Cancer can also be caused due to replication errors, exposure to chemical carcinogens, radiations and sometimes also due to viral infections[1].

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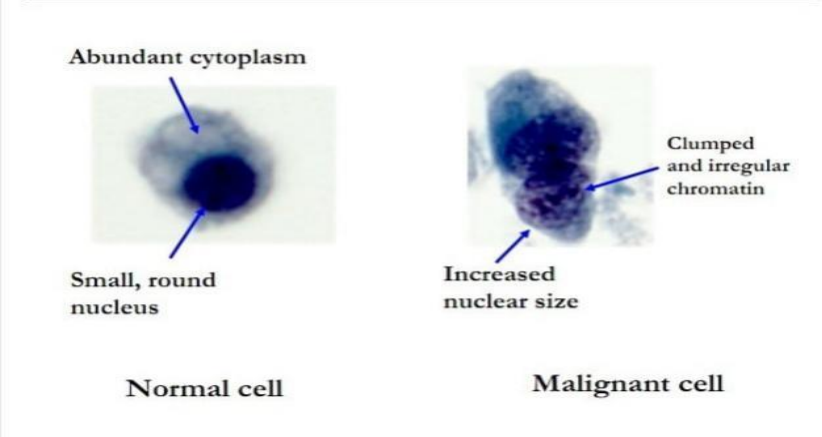

Figure: 1: Cellular growth of cancer formation

Types of Cancers [2]

Cancers are of two types, they are benign tumor and malignant tumor. Among these benign tumor does not migrate to other place from the place of formation and they can be removed by surgery, whereas malignant tumors are having capacity to migrate to other parts of body which is primary danger with malignant tumors. If the illness reaches to any of the body's vital organs it would be fatal sometimes. Malignant tumors cannot be removed easily by surgery and reoccurrence is seen even on removal of these types[4]. They need to be treated by chemotherapy, radiation or by other means.

Types of Cancer

Carcinoma:

Cancers arising from epithelial tissues like breast, body cavity, skin and prostate.

Sarcoma:

Cancers arising from supporting tissues or any connective tissues like blood vessels, bone, cartilage, fat, muscles and nerves.

Lymphomas & Leukemias:

Cancers arising from blood-cells forming tissues i.e. lymph nodes, spleen & bone marrow.

STEPS INVOLVED IN CANCER FORMATION[2]

Initially tumor cell evolution takes place due to any of the genetic mutation, the genetically altered cell and its off springs seem to be normal, but reproduce excessively which is referred as hyperplasia. The offspring of cell proliferates and appear abnormal in shape called as dysplasia. The genetically altered cell continues to grow abnormally and if tumor mass does not invade to other parts, it is called benign tumor or in-situ tumor. When the tumor mass invades underlying tissue and moves into blood or lymph and generate blood supply for the newly formed cells it may migrate to other parts of the body called as malignancy. The tumor mass develops blood

supply by the process called angiogenesis. Cancer cells differ from normal cell in adhesion; they even survive for years if not adhere among themselves or to the extracellular matrix without undergoing cell suicidal or apoptosis. This is a challenging aspect in targeting of drugs to tumor

Site Specific Drug Delivery

Site specific drug delivery is classified into three types according to the specificity levels achieved in the delivery process[3]:

Organ Targeting: drugs are delivered to the individual organs or tissues.

Cellular Targeting: drugs are delivered to the specific cell type within a tissue.

Intracellular Targeting: drugs are delivered to the different intracellular compartments in the target cells by special transport pathways. The strategies of tumor targeting are discussed as follows:

1. Immunotherapy strategies
2. Multi-drug resistance targeting
3. Novel drug delivery systems
4. Other targeting strategies

IMMUNOTHERAPY STRATEGIES

Immunotherapy comes under passive targeting; it is aimed to attack disease with defense mechanism of body by using tumor antigens, antibodies, recombinant antibodies and monoclonal antibodies. [3]

Tumor antigens:

These are popularly known as tumor vaccines[7], they exhibit prompt immune response in individuals by activating their own immune system. Whole tumor cell can be used for this purpose. It can be given in extract form or whole cell can be used in an inactivated form. Nucleic acids like DNA & RNA coding for tumor antigens can also be used. Vaccines are having the advantage of showing reproducible production of antibodies against the tumor forming cells on subsequent attacks and also boost up the immune system.

Antibodies:

They bind to the antigens of tumor cells and by this they are susceptible to destruction by the host's immune system. They are further helpful in targeting blood vessels that supply to tumor, also to target its connective tissues. They can be used as a guided missile to recognize and deliver the therapeutic compounds to the tumor sites. Antibodies also acts as toxins which inhibit protein synthesis in tumor cells and in turn inhibit the tumor growth, they also trigger cytokines & inflammatory mediators which are helpful in these cell destruction[8].

Antibodies with prodrugs:

When prodrugs are attached to tumor specific antibodies, they are converted to active moiety by enzymatic action and they show action against the tumor cells. Antibodies often linked directly with chemotherapeutic agents by which direct targeting of agent to the tumor cell can be achieved and it reduces associated side effects and toxic effects[9]. Advancement in usage of antibody is antibody directed enzyme prodrug therapy (ADEPT), it utilizes the principle of localization of intravenously administered antibody with enzyme as a conjugate in the tumor tissue and the enzyme activates the prodrug within the tumor.

Recombinant antibodies:

Recombinant antibody fragments can be used for development of anti tumor strategy. Generally immunoglobulin

Multi Drug Resistance Targeting[4]

Multi drug resistance is the problem associated with chemotherapy, the initial and subsequent chemotherapy allows tumor to develop secondary resistance. After getting resistance by the tumor cells additional chemotherapy will induces toxic effects in subjects without reducing the tumor growth. Tumor cells with multi drug resistance over expresses an energy dependent drug transport protein commonly referred as pglyco protein (p gp). This over expression leads to lowering of drug accumulation within the tumor cells since the cell is having ability to pump out hydrophobic anti tumor drug molecules with p-glyco protein pump. P gp further detects and expels the drug and it just acts like a hydrophobic vacuum cleaner. Specific class of drugs known as multi drug resistance reversal agents can be used to overcome these problems, eg: Doxorubicin[3]. These reversal agents acts by binding to P-glycoprotein and they block this channel, so that the drug is allowed to slip into the tumor cell and they can inhibit or kill the tumor cells.

Multi drug resistance reversal agents are often used in conjunction with liposomes for appropriate targeting due to the below stated reasons.

- Negatively charged phospholipids like phospholipids or cardiolipin in liposomes directly regulate the p gp transporter.
- Liposomes provide sustained high levels of drug to the resistant cells over longer periods of time.
- After endocytosis of drug loaded liposomes by lysosomes, lysosomes protect liposomes from action of p gp and avoid immediate contact with the transporter located at the plasma membrane.

Novel Drug Delivery Systems[4,5]

They are the promising drug delivery system that provide site specific targeting of drug to the tumor cells, elicits therapeutic concentration of drug at the effected region without affecting the normal system. They include vesicles like liposomes, niosomes, particulate systems like microparticles and nano particles. The primary aim of these systems is to ensure safety and to improve efficacy along with patient compliance. Of all novel drug delivering systems liposomes are widely selected for targeting in neoplastic disorders owing to its smaller size, compatibility with tissues and many more advantages.

Liposomes[6]

They are helpful for passive targeting to different tumors because of their longer circulatory half lives and they moves into tissues easily due to their vascular permeability due to low size and lipid nature. Specially engineered liposomes called stealth liposomes or pegylated liposomes which are sterically stabilized and coated by polyethylene glycol are used for longer circulation and increased permeability for movement into the vascular endothelium of the tumor cells.

On the other hand liposomes can be used in active as well as in passive targeting to the affected cells. Passive targeting can be achieved by using conventional liposomes and immunoliposomes. Immunoliposomes are produced by attaching liposomal surface to the antibodies developed against the tumor cells or against the specific surface antigens present on the tumor vascular endothelium. Active targeting can be achieved by usage of ligand mediated targeting in which ligands are developed against cell receptors or antigenic determinants which are expressed exclusively on the tumor vasculature. The ligands include antibodies, glycolipids, glycol proteins, polysaccharides, proteins and immune regulatory molecules. Physicochemical strategies can also be utilized for targeting of liposomes, in this drug-carrier is given to the body and they release the drug only when exposed to specific micro environments such as change in pH, temperature or subjecting to the external condition like light, magnetic fields. Examples of liposomes targeting by physicochemical strategies include pH sensitive liposomes, thermo sensitive liposomes, photo activated liposomes and magneto liposomes.

pH sensitive liposomes

The pathological tissues of tumors have ambient pH which is considerably lower than the normal tissue. pH sensitive immuno liposomes can deliver the drugs directly to the cytoplasm of the tumor cells. Eg: dyes like calcinin, drugs like methotrexate.

Thermo sensitive liposomes

Thermo sensitive liposomes are positively charged liposomes having encapsulated paramagnetic materials often referred to as magneto-cationic liposomes. They release the drug on application of external heat, these thermo sensitive liposomes used as effective tools for hyper thermic treatment of solid tumors.

Photo activated liposomes

Photo activated liposomes consist of photo sensitive polymer in the external surface of liposomes and they release the drug from the liposomes on external application of light and they are helpful for the localized delivery of drug to the tumors.

Magneto liposomes

Magneto liposomes are having iron containing particles like magnetite in the liposomal surface. They release the drug on external application of magnetic field[12]. This strategy is helpful in localization and controlled delivery of drug to the tumors. Magneto responsive thermo sensitive liposomes are modification of magneto liposomes and they release the drug in response to magnetic modulation and hyper thermia. Conventional liposomes are up taken by Reticulo Endothelial System (RES) and they are used to target the reticulo endothelial system organs like liver, lungs[13] and spleen, whereas stealth liposomes are used to target non-reticulo endothelial system organs and they are having longer circulatory half-life since they are having capability to escape the circulating scavengers and degradation by these organs[14].

Niosomes[7]

Niosomes are the vesicles similar to liposomes and along with lipid a non-ionic surfactant is employed in this formulation. They are having similar properties of entrapment of drugs and they are stable compared to other formulations and they show varied drug distribution characters and release characters since the surfactant used is of non biological origin and it escapes clearance of phagocytic system and shows a prolonged release characters.

Particulate System in Chemotherapy[7]

It is the most promising application and by this we can achieve targeting to the tumor tissues. Particulate system includes nanoparticles and microspheres. By intravenous administration accumulation of these particulate systems in the tumors is favored. The reason beyond this is presence of enhanced endocytic activity of immune system and leaky vasculature of the tumor cells.

Stealth microparticles or nanoparticles can be prepared by coating them with polyoxyethylene or with dialkyl polyoxyethylene and phospholipids they are used to target the non reticulo endothelial system organs whereas non stealth or conventional microparticles or nanoparticles

can be used to target the reticulo endothelial systems. Polymers like polylactide, polyglycolide, polylactide-co glycolide and polyvinylpyrrolidone (PVP) are used in nano particles preparation along with polyalkyl cyano acrylates, eg: Taxol in PVP nanoparticles. Particulate system can be used for site specific targeting by coating them with antibodies. In this anchoring of target specific antibodies to the particulate system is more helpful in targeting. Monoclonal antibodies can be fixed on to the surface of particulate system by direct absorption or by covalent linkage. Following are the examples of drugs that are targeted by nanoparticles.

- Doxorubicin in polyisohexyl cyanoacrylate nanoparticles
- Doxorubicin in polyalkyl cyanoacrylate nanoparticles
- Mitoxantrone in polybutyl cyanoacrylate nanoparticles

Other Targeting Strategies

Other targeting strategies include targeting the angiogenesis, usage of chemo embolization and by receptor level targeting.

Angiogenesis

Angiogenesis means formation of new capillaries by the tumor cells for their existence, as the tumor mass increases the new capillaries starts in the form of vascular sprouts and gradually develops into new capillaries. This process is also called as neovascularization. It continues between cells and passes to the other parts also, the danger associated with angiogenesis is that malignancies pass over the body by these newly formed capillaries and may enter the systemic circulation which might migrate to the vital organs of the body. Angiogenesis inhibitors like thrombospondin & angiostatin can be used to overcome the angiogenesis. They inhibit the new blood vessel formation, limits the tissue perfusion, inhibits vascular sprout generation, also interfere with endothelial growth factors which stimulates tumor growth[8].

Chemo Embolization: Intra-Arterial Infusion Chemotherapy

In this chemotherapeutic agent with novel drug carriers like microcapsules and liposomes can be used. Implantable equipment can be used for intra-arterial use. In this biodegradable particles are administered to target to the liver tumors i.e. drugs are given in an injection form with the help of a catheter into the artery that directly leads to the tumor. This can be used for continuous infusion or for a single use. The solution on reaching the target as a bolus localizes in the target organ and shows reduction in the tumor growth. This way is helpful to treat the patients for a longer time and if needed more frequently with less discomfort[9].

Conventional Therapy[9]

The conventional therapeutic methods include chemotherapy and radiation therapies. Chemotherapy includes administration of antineoplastic agents which kills tumor cells and also all actively growing cells which results in gastric ulceration and bleeding, anemia, alopecia, destruction of regenerated cells of lungs, liver and maintenance of higher concentration of drugs in plasma which results in unwanted affects and adverse effects of the drugs. Radiation is given directly to the site of tumor which easily damages the DNA of cells, exposure to the radiation may also affects some of the non-cancerous tissues[9].

CONCLUSION

The current review highlights various modalities which are under study to overcome the problems associated with conventional therapies, focuses on selective targeting of drug moiety to the desired affected tumor cells[20]. A more thorough in-depth study regarding uptake by various tumor cells and their expressions is needed for refinement of the targeting strategies. Targeting by novel carriers deserves the attention as such carriers offers the possibility of targeting a wider range of therapeutic systems. Further a combination therapeutic regimen utilizing advantages of localized or direct administration and tumor specific delivery systems is of significant importance to the cancer patients. Recombinant technologies with the bio-pharmaceutical industry is producing various vaccines and is studying gene level targeting in tumor therapy which will be a trend setting in the modern pharmaceutical erena.

REFERENCES

1. Bae YH and Park K. “Targeted drug delivery to tumors: myths, reality and possibility” Journal of Controlled Release; 2011; 153(3):198-205.
2. Deepak K, Deepti J, Vivek S, Rajendra K and Patil AT. Cancer therapeutics opportunities, challenges and advances in drug delivery. Journal of Applied Sciences. 2011;1(9):1-10.
3. Salmad A, Sultana Y and Aqil M. Liposomal drug delivery systems-an update review: Current Drug Delivery; 2007;4(4):297-305.
4. Ramon M, Esther V and Antonio V. Targeting in cancer therapies. Journal of Medical Sciences. 2016;4(6):1-2.
5. Jaffe R, Alashari M, Nour B, Tzakis A, Dickman. “The association of Epstein-Barr virus with smooth-muscle tumors occurring after organ transplantation”: N. Engl. J. Med; 1995; 332 (1): 19–25.
6. Lichtenstein P, Holm NV, Skytthe A, Hemminki K . “Environmental and heritable factors in the causation of cancer”: N. Engl. J. Med;2000; 343 (2): 78–85.

7. Shen L, Buckmeier J, Alberts DS, Hamilton SR, Issa JP . "MGMT promoter methylation and field defect in sporadic colorectal cancer": J. Natl. Cancer Inst; 2005; 97 (18): 1330–8.
8. Mokarram P, Zamani M, Kavousipour S, . "Different patterns of DNA methylation of the two distinct O6-methylguanine-DNA thioltransferases (O6-MGMT) promoter regions in colorectal cancer": Mol. Biol. Rep; 2013; 40 (5): 3851–7.
9. Moolenaar F,Huizinga T, "Biopharmaceutics of rectal administration of drugs in man. Absorption rate and bioavailability of phenobarbital and its sodium salt from rectal dosage forms" :International Journal of Pharmaceutics; 1979; 4(2); 99-109.
10. McKeran RO, Firth G, "A potential application for the intracerebral injection of drugs entrapped within liposomes in the treatment of human cerebral gliomas": Journal of Neurology, Neurosurgery, and Psychiatry;2010 ;48(12); 1213-1219.