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Review Article

Dendritic scaffolds as novel carriers for cancer cell targeting

Narasimha Rao B[1*], Ravindra Reddy K[2], Chandra Sekhar K.B[3]

[1]PRRM college of Pharmacy, Kadapa, Andhra Pradesh, India
[2]CES college of Pharmacy, Kurnool, Andhra Pradesh, India
[3]Oil Technological Research Institute, JNTUA, Anantapuramu, Andhra Pradesh, India

ABSTRACT

Cancer is a complex disease that is caused primarily by environmental factors. The cancer -causing agents (carcinogens) can be present in food and water, in the air, and in chemicals and sunlight that people are exposed to. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. Cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Cancer is usually treated with chemotherapy, radiation therapy and surgery. Above mentioned treatment methods are affecting the normal cells without properly targeting the specific cells of tumor. Due to the reason various novel drug delivery systems were implemented. Recent advances in drug design have led to the development of new small molecular weight chemotherapeutic agents, peptide and protein molecules that can be used for the treatment of cancer. However, transformation of these drug candidates in to actual therapies with well-defined dosage regimen remains a significant challenge due to the limited ability to selectively deliver these drug molecules in to the cytoplasm of cancer cells. Dendrimers are novel synthetic polymers, which can be used as universal carrier on creating systems for drug delivery of cytotoxic drugs to solid tumors. These carriers have unique characteristics including monodispersity, surface functionality along with highly defined size and structure. This makes these polymers attractive candidates as carriers in targeting the cancer cells.

Keywords: Dendrimers; Cancer cells; Drug delivery; Targeting; Tumor; EPR effect; Biomarkers.

INTRODUCTION

Cancer which is also known as a malignant tumor is a group of diseases involving abnormal cell growth, with the potential to invade or spread to other parts of the body (Kytai Truong Nguyen *et al*., 2011). So, an anticancer agent used should target the tumor cells specifically without affecting the normal healthy cells. But the conventional cancer chemotherapy used today often suffers from problems like non-specificity and poor water-solubility. If the cancer drugs lack specificity they might exert side-effects on the healthy normal tissues besides killing cancerous cells and poor water solubility limits the bioavailability of drugs. In order to overcome these problems, novel polymeric multifunctional dendritic carrier systems have been introduced with the aim of developing an efficient targeted delivery system that overcomes poor water solubility of the drugs and drug leakage during circulation (X. Kong et al., 2014).

Dendrimers are a new class of synthetic polymeric materials that are highly branched, three dimensional nanosized structures with very low polydispersity and high functionality. The surface of dendrimers poses a great impact on its physical and chemical properties (Dwivedi Devendra Kumar *et al*., 2014). Dendrimers possess empty internal cavities and terminal functional end groups that facilitate to their high solubility and reactivity. Dendrimers were first discovered in 1980's by Donald Tomalia and co-workers. The word dendrimer has been originated from the Greek words 'dendron' meaning 'tree' and 'meros' meaning 'part'. (Priya *et al.,* 2013).

* Corresponding Author
Email: simham1985@gmail.com
Contact: +91-9162592004
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Structure of Dendrimer

Dendrimers possess 3 distinct architectural units.

A central core: It is the innermost part of the dendrimer and is generally hydrophobic in nature.

Internal layers: To the core material, other layers get attached radially by a series of chemical reactions to give out a spherical branching structure. These layers are referred to as generations. This branching process is repeated till the desired generation dendrimer is produced (Reshama Tambe *et al.*).

An exterior layer: It is the outer most part of the dendrimer. Terminal groups are attached to the exterior layer and these groups influence the physical and chemical properties of the dendrimers.

Synthesis of Dendrimers

Dendrimers can be successfully synthesized by the following ways:

a. Divergent growth

b. Convergent growth

Divergent growth

This method was first introduced by Tomalia. Here growth of a dendrimer originates from the core material (inside) and proceeds out as generations by a series of reactions between dormant and reactive groups. The reactions continue till a high or desired generation dendrimer is obtained.

Convergent growth

In convergent growth, Dendrimers are built from the terminal end groups and gradually proceed inwards to the core. As the generations increase, the polymeric branches also increases and gets attached to the core material finally giving out a complete dendrimer molecule (Patel *et al.,* 2010). The convergent method is more advantageous because the purification of final product is easy and we can minimize the defects in the final product.

PEGylation of Dendrimers

PEGylation is the polyethylene glycol conjugation or polyethylene glycol linking with the dendritic system. PEGylation technology was first attempted in the early 1970's by Davis and Abuchowskyon.

Although the Dendrimers possess vast applications in the field of medical sciences, but their use has been restricted due to drug leakage, RES uptake, immunogenicity, stability, hemolytic toxicity etc. PEGylation of Dendrimers can overcome these limitations and increase the solubility of hydrophobic drugs. Generally, PEG is water-soluble and this water-soluble agent when coupled with Dendrimers resists its recognition by opsonins thereby increasing circulation time of Dendrimers in body. An ideal PEGylated dendritic drug-carrier system should be non-toxic, non-immunogenic and biodegradable and should allow appropriate biodistribution and tissue targeting within the body. PEGylation process leads to changes in the physico-chemical properties like hydrophobicity, electrostatic binding, confirmation etc. These changes increase retention of therapeutic agent within the dendritic system. PEGylation also influences the binding of the therapeutic moiety to the receptors of the target site thereby influencing its absorption and distribution mechanisms (Bhadra *et al*. 2003).

Purpose of PEGylation: The main purposes of PEGylation include

- Alteration of pharmacokinetics and biodistribution of Dendrimers by increasing its circulation time due to decreased RES, liver, spleen and macrophageal uptake.
- To decrease the toxicity of Dendrimers by masking their peripheral groups like NH_2.
- Alteration of solubility parameter of Dendrimers and render them more soluble.
- Controlled and sustained delivery of drugs safely to the target site.
- To increase drug's stability
- Enhanced protection from proteolytic degradation

Dendrimers – different ways to approach cancer cells

As we know, cancer is a disease with an ability of spreading to other healthy tissues vigorously. Drug delivery to such tumor cells is a risky issue. Conventional cancer chemotherapy involves higher doses of therapeutics and such a higher dose may affect the other healthy tissues also. Additionally, there are many physiological barriers restricting drug delivery to these cells include vascular endothelial pores, heterogeneous blood supply to the tumor, long transport distances from vessels to the tumor cells, RES uptake and multi - drug resistance etc. These barriers make tumor-drug targeting problematic. So, therefore an ideal therapeutic drug carrier system should be one that avoids immune recognition and targets specifically the tumor cells without damaging the other healthy cells. Dendrimers with their properties like encapsulation, target specificity, PEGylation and covalent linkage of the drug moiety to the dendrimer makes them attractive vehicles in the cancer targeted drug delivery (James Baker *et al.,* 2005).

EPR effect

Generally tumor cells show enhanced permeability and retention (EPR) effect. This is the unique structural change of tumor vasculature which is based on the patho-physiological conditions like limited lymphatic drainage, increased permeability to lipids and macromolecules and extensive angio-genesis that results in hyper-vascularization. These features enable the tumor cells to meet the metabolic requirements of rapidly growing tumors. Here, Dendrimers make use of this property to facilitate the drug delivery to the tumor cells (Srinivasa-Gopalan Sampath Kumar *et al.,* 2007). This EPR-mediated targeting can be achieved by controlling the size and physico-chemical properties of Dendrimers.

Role of biomarkers

Another approach to target the tumor cells is the use of biomarkers as selective targets. Biomarker is a measurable indicator of presence of disease or abnormality. Practically, a biomarker is a substance secreted or some specific response of the body to the presence

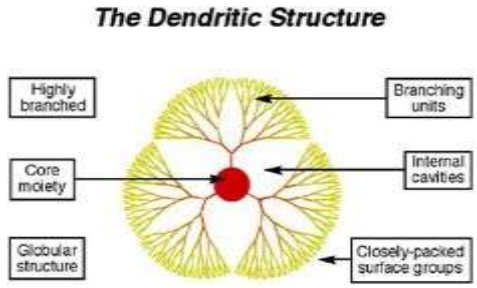

Figure 1: Structure of Dendrimer

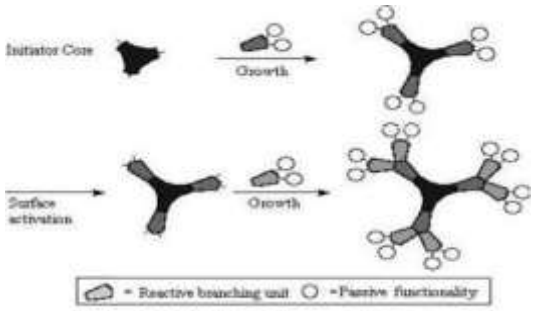

Figure 2: Divergent growth of dendrimer

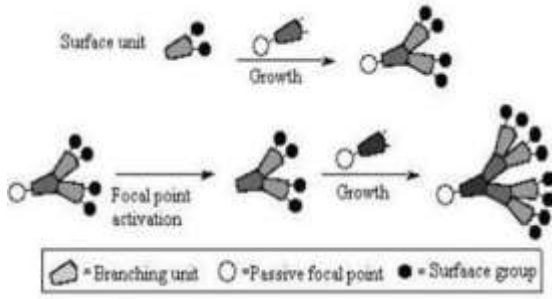

Figure 3: Convergent growth of dendrimer

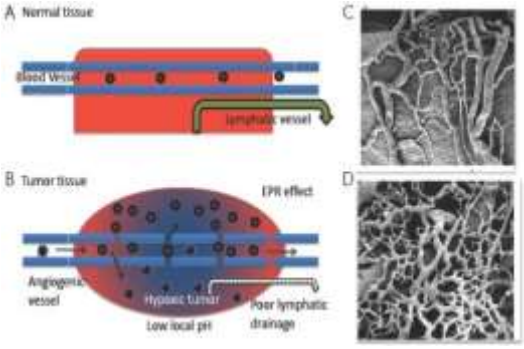

Figure 4: Role of EPR effect of tumor cells in tumor targeting

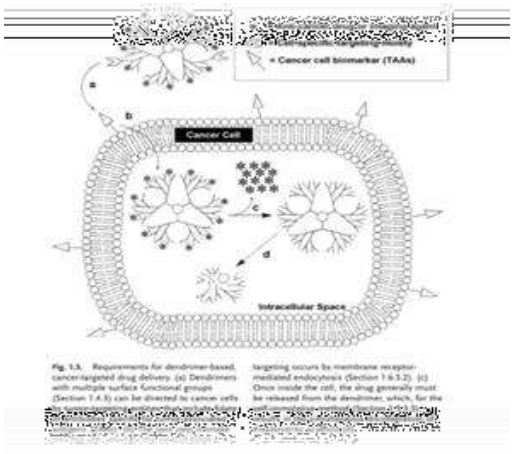

Figure 5: Role of biomarkers in targeting cancer

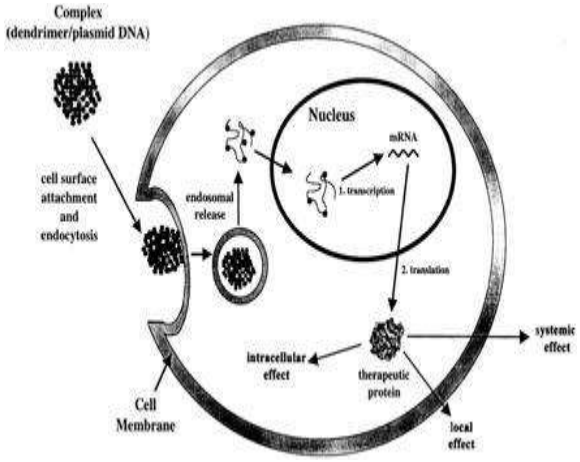

Figure 6: Dendrimers in gene therapy

of cancer. Biomarkers have a great impact in the oncology field (Srinivasa Rao B *et al.,* 2013). A tumor can be detected by the presence of biomarkers and it provides some valuable information that helps in the tumor diagnosis, treatment etc. Generally most targeted drug delivery strategies require the therapeutic agent to get attached to the tumor cell directly. Dendrimers, with their multi-functional surface architecture allows the inclusion of ligands like folic acid, oligosaccharides, polysaccharides, oligopeptides as well as monoclonal antibodies within them. These ligands are cell specific targeting moieties that are specific to biomarkers. Ligands detect and attach themselves to the biomarkers. This approach directs or provides access to the therapeutic agent to the target cells. Once the drug loaded dendrimer reaches the target site, the next step is its intake into the target cell by mechanisms like Receptor – Mediated Endocytosis. Inside the cell, the drug must be released from the dendrimer to exhibit its therapeutic action and simultaneously disintegration of the dendritic scaffold from the body (Srinivasa -Gopalan Sampath Kumar et al., 2007).

Folate is a small molecule, used primarily as a tumor targeted ligand. Its use in cancer treatment is wide because the membrane-bound folate receptor is over-expressed on human cancer cells present in ovary, lung, breast, kidney, brain and endometrium and absent in normal tissues. Monoclonal antibodies are the most elegant and demanding ligands that selectively directs the therapeutic agents to the cancer cells. Monoclonal antibodies recognize and bind to the tu-

mor associated antigens that are present on the cell surface and TAA's are specific to the antibodies.

DENDRIMERS BASED CANCER THERAPIES

Dendrimers in cancer imaging

Contrasting agents have become an important tool in the modern diagnostic field. The structural architecture of Dendrimers provides multiple sites on its periphery allowing contrasting agents to bond with them. One dendrimer molecule can host up to 24 contrasting agents depending upon the dendritic generations thereafter providing higher signal to nose ratio.

Dendrimers are conjugated to contrasting agent li ke Fluorochromes. Fluorochrome is a novel contrasting agent that targets only affected cells. As dendrimer-fluorochrome complex enters the cell, it is possible to characterize various aspects like, cell targeting, surface binding, cellular uptake and internalization and even sub-cellular localization. Gadolinium is another contrasting agent, conjugated to folate receptors or tumor associated antigens in order to target the cancer cells.

Dendrimers in Photodynamic Therapy

Photodynamic therapy is a treatment that involves the usage of drug called photosensitizer or photosensitizing agent and a particular type of light. When this drug is exposed to specific wavelength of light, it produces a certain form of oxygen that has an ability to kill the nearby cells.

Generally Photosensitizers when administered enters each and every cell but they have longer retention times in cancerous cells. After 24-72 hours, photosensitizers get cleared off from the normal healthy cells but remains in the cancerous cells. At this moment specific radiations are allowed to pass through the cells. The photosensitizer in the tumor cell absorbs the radiation and produces certain form of oxygen that kills or destroys the nearby cells. The use of this therapy is limited because there is a chance of photosensitizer present in the normal cells that might get destroyed after radiation exposure.

Dendrimers play a vital role in pharmacodynamic therapy. Dendrimer architecture facilitates the delivery of the photosensitizer to the tumor cells by recognizing specific receptors on them. Dendrimers fasten the treatment without waiting for the elimination of drug from the normal cells.

Boron Neutron capture therapy

Boron Neutron Capture Therapy involves delivery of sufficient number of stable non-radioactive isotopes of Boron to the tumor cell. As the boron gets accumulated in the tumor cell, a low energy beam of neutrons is given to the stable boron. After capturing the neutron, boron disintegrates producing high energy heavy charged particles that destroys cells present close to it, mostly cancer cells. Thus effectiveness of treatment depends upon deposition of boron derivatives into the target cell. Dendrimers here are useful in specifically depositing or carrying the boron derivatives to the target cell.

Gene therapy

Gene therapy is one of the methods used to treat cancers. Dendrimers are now even used as vehicles or vectors for transferring genetic material to the targets. Dendrimers offer many advantages over viruses as carriers of nucleic acid materials like ease of production, low cost, less toxic, ability to carry larger amount of genetic material than viruses. Dendrimers have the capacity of tumor transfection i.e. they can introduce nucleic acids into cells by non-viral methods in the tumor cells. Once dendrimer gets inside the body, the genetic material releases, recognizes and kills the cancer cells (Subha Shankar Ghosh., 2010).

DNA-Dendrimer assembled cancer targeting

Conjugating different molecules to a single dendrimer may result in problems like decrease in yield, decreased water solubility because of hydrophobicity of attached molecules or functional groups etc. In order to overcome these problems and to improve the efficient targeted drug delivery, dendrimers are conjugated to bio-compatible DNA. Here two differentially functionalized dendrimers are conjugated using a DNA linker. One dendrimer holds or encapsulates the folate ligand that selectively targets the folate receptors of tumor cells while the other dendrimer holds imaging agent or fluorescent dye (James Baker R *et al.,* 2005).

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