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Importance of Nanoparticles in Targeted Drug Delivery System for Treatment of Cancer: A Brief Review

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Review Article

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ABSTRACT

This review documents the changing perspectives on the function of nanoparticles their synthesis and role in the targeted drug delivery to the tumor cell receptor in the study of human tumor biology. Cancer biology and therapeutics today is an topic of research interest and a leading medical issue around the globe, this document present a view of appreciation towards the lately developed methods in cancer therapeutics involving the dominant role played by the nanoparticles derived or synthesized from different sources and functionalities as of in targeted drug delivery system as a conjugate to the drug and acting as a vector synthesized and designed to ligate to specific receptors. The different aspects involved into the synthesis of the Nano carriers such as its size, shape, surface charge, density, have a tremendous effect upon the nature and function of the Nano carrier in in vivo and the overall effect of it as an effective drug.

INTRODUCTION

The use of carriers to guide chemotherapeutic drugs to the targeted cancer cells has become an issue of crucial and grave importance into the field of oncology and therapeutics. The clinical success, as well as the ease with which these vectors promise to function has aroused interest and hopes among researchers and medics around the world. The system is based on a method that delivers a certain amount of a therapeutic agent for a desired period of time to the targeted cells or a tissue within the body. This helps maintain the required plasma and tissue drug levels in the body, thereby preventing any damage to the healthy tissue by the drug. Ultrasound has evolved from being primarily used for diagnosis into treatment of diseases (e.g. cancer) by delivery of drugs [1]. The major challenge for the vectors is for not become a thwart themselves such as in obstructing the binding or rendering the drug incompetent for binding at the specific receptor and least of it is not to react by themself into the pathways of drug inducement system to give rise to side effects. Thus the drug delivery system is highly integrated and delicate process that requires various disciplines, such as chemists, biologists, and engineers, to work together to optimize and run this system in a safe and precise manner.

CANCER CHEMOTHERAPY

Destroying biological pathogens is easy. The point is how to destroy them while sparing the host. This is especially obvious when dealing with cancer. Despite recent progresses in the diagnosis and treatment, lung cancer still remains the leading cause of death due to tumor where worldwide Gastric cancer is the fourth most common malignant disease and the second leading cause of cancer mortality worldwide [2 - 5]. To critically evaluate treatment wait times in CRC (colorectal cancer) patients and identify clinical and systemic barriers to treatment even the complexities of cancer, chemotherapy frequently fails for many unknown reasons. Recent technological advances, including single cell genomic technologies, Anti-mitotic drugs target the reorganization of microtubules essential for proper cell division and proliferation. The epigenetic machineries have proven roles in a wide variety of cancers[6]. The

epigenetic machineries have proven roles in a wide variety of cancers. For patients with metastatic or recurrent GC, the evidence supports the use of chemotherapy to prolong survival and maintain quality of life Advances in the treatment of ovarian cancer over the past decade, have led to emphasize the concept of managing ovarian cancer as a chronic disease [7 - 10].

If a cell is attributed to an outer electric field, the highly resistive membrane will accumulate charges like a capacitor. More recently, NEK1, the first cloned mammalian NIMA related protein kinase drug discovery in the ovarian cancer arena continues to launch important new clinical trials. Many biologic agents are being studied in phase II and phase III clinical trials for recurrent disease [11, 12]. A broad spectrum anticancer triterpene that exhibited antiproliferative effects at nanomolar range against almost all of the cell lines in the NCI-60 which may serve as a potential lead compound for the development of new anticancer drugs. Angiogenesis plays a key role in the survival and invasion of cancer cells, thus making anti-angiogenesis a widely researched area of cancer care [13 - 15]. Anti-angiogenesis therapy had been expected to both prune the immature vessels and normalize tumor vessels by decreasing interstitial fluid pressure and increasing the delivery of drugs and oxygen monotherapy is recommended in the treatment of relatively slowly progressing advanced colorectal cancer. Breast cancer is not only the second most prevalent type of cancer but also most frequent cause of cancer deaths in women [16 - 20].

Psychological problems like depression, anxiety, poor self-image and use of unhealthy coping strategies affect quality of life of breast cancer patient. In latest therapeutics the Double-Strand Breaks (DSBs) can be promptly recognized by the Ku70/Ku80 heterodimer or the MRE11-RAD50-NBS1 (MRN) complex [21 - 23]. The MRN complex helps to activate and recruit ATM, In the past decades, chemotherapy has become the major therapeutic approaches in several human life-threatening diseases including microbial infections Dose dense carboplatin and paclitaxel regimens are increasingly being used to treat advanced serous gynecological malignancies (ovary and uterus) in the adjuvant and relapse setting. More recently drug resistance has become a devastating problem in cancer chemotherapy because drug resistant cancer cells are harder to kill with the same drug [24 - 28].

SCOPE OF REVIEW

One of the most important properties of targeted drug delivery of nanoparticle to be controlled in the particle functionality is the cytotoxicity of nanoparticle. Nanoparticle properties for therapeutic applications are governed by several factors such size and shape, surface charge of the nanoparticles etc.

Surface charge

Surface charge along with charge density and charge polarity plays a major role in the delivery and cellular uptake action for a nanoparticle. Studies have shown that charged nanoparticles are more cytotoxic than neutral charged nanoparticles [29]. Among charged nanoparticles, positive forms are said to be more cytotoxic than negatively charged nanoparticles. Use of Silica-Gold Core Shell Structured Nanoparticles is said to have required surface charge for the targeted drug delivery [30]. Cellular uptake of nanoparticle is also influenced by charge density. Cellular uptake involves electrostatic interactions between positively charged nanoparticle and membrane which favors its adhesion onto surface of cell. On the other hand, even small but positively charged nanoparticle (2 nm) can alter the cell membrane potential as well as inhibits its proliferation and induces fluidity of the membrane. Cationic charged nanoparticles such as super paramagnetic iron oxide particles, lipid particles, poly (lactic acid), chitosan, gold and silver particles are taken up by the cells at a higher level than the anionic nanoparticles magnetic nanoparticles show remarkable phenomena such as superparamagnetism[31].

Surface nature and chemistry

Surface chemistry of a nanoparticle is an important factor during clearance or uptake in circulation. For long circulation half-life nanoparticles must escape from macrophages. Hence, residence time or circulation time is the major factor considered for effective designing of nanocarriers [32]. To have long circulation half-life for the nanoparticles is essential as to escape from macrophages effectively therefore, the important factor in the designing of the nanocarriers is residence time or circulation time. In cancer therapy, passive targeting requires long circulation because of the EPR effect observed in the tumor vasculature after multiple passes, in order to achieve this, drug degradation should be minimal for the designed nanoparticles therefore the surface modification is an effective requirement to make the nanoparticle carry loaded drug to the targeted site [33]. It has been reported as an effect of these changes the Cells undergo apoptosis display typical condensed morphology, namely cell shrinkage, chromatin condensation and nuclear fragmentation [34]. Drug delivery is to be profoundly benefited by use of Magnetic Nanoparticles (MNPs) due to the ability of these particles have to target a specific site, such as a tumor, thereby enhancing drug uptake at the target site and reducing the systemic distribution of the drug compounds in vivo and, resulting in effective treatment at lower doses [35].

The blood half-life of nanoparticles is said to be dependent on the surface hydrophobicity of nanoparticles. Nanoparticle's surface hydrophobicity determines the amount of proteins (opsonins) adsorbed on to the surface. Particles which are more hydrophobic suffer more opsonizationit was reported that human serum albumin (HSA) adsorption onto the nanoparticles decreased their specific surface area and porosity [36]. Past studies have reported the Poly Ethyle Glycolysation (PEG) and binding of Polyphosphate and Glucose with the nanoparticles as hydrophilic blocks [37, 38]. Increases the circulation time by escaping through immune cells (opsonisation) as for the past studies reported that PEG (Polyethylene glycol) prevents aggregation of the nanoparticles, helps in stabilising the nanoparticles, providing a neutral surface charge to nanoparticles, nanoparticles and escape from clearance by preventing from opsonins and also has advantages over other nanocarriers such as excellent biocompatibility, biodegradability and mechanical strength for these nanoparticles [39]. For effective modification of the surface, length and density of the PEG plays vital role. PEGylated mesoporous silica nanoparticles presents low systemic toxicity in healthy mice and enhanced tumour inhibition rate [40].PEG shields the inner core of nanoparticle from blood proteins by forming a brush layer on the surface of nanoparticles. The access of encapsulated drug is restricted to the enzymes by modification of the nanoparticle surface therefore, improving pharmacokinetic profile and reducing non-specific toxicity. Surface modification chemistry aims at specificity by targeting, ligand design is used in therapeutics, imaging reporter molecules, and controlled release Polymer-Coated Hydroxyapatite Nanoparticles [41].

Effect of size and density

The functional properties of the particle like its uptake, residence in circulation, adherence, degradation as well as clearance is influenced by its size and density. Size is responsible for the movement of the nanoparticles inside the tissues. It has been known that the movement of the particles inside tissues is dependent on the size as their movement can be sterically hindered in extra-cellular matrix due to which acidic and cysteine rich secreted protein targeted nanoparticles and BTC(Biodegradable Thiolated Chitosan) nanoparticles gains popularity because of their high mucoadhesiveness and extended drug release properties [42, 43]. Based on the relationship between particle size and its curvature (for spheres), size of the nanoparticles along with surface chemistry, may also affect opsonization. It is well known that small size of targeting nanoparticles play vital role in that accumulated inside the tumors by EPR effect that in turn depends on the extravasation through the gaps in tumor vasculature. Studies have reported that ultra-small gold nanoparticles exhibits uniform distribution within the tumor tissues due to their ability to diffuse through tissues, smaller nanoparticles tend to shown better circulation and accumulation but the uptake is poor. Particle diameter and size can be controlled by variation of different physical and chemical parameters.

The size and density of a particle guides its way inside a bloodstream, diffusion in cells or membranes, air-passage or gastro-intestinal tract densely dispersed capsaicin-loaded trimethyl-chitosan

nanoparticles (CL-NPs) has an effective anti-cancer agent which efficiently induced apoptosis in human HepG2 hepatocarcinoma cells [44]. Significant attempts were made in order to obtain the nanoparticles in the size range of 10-50 (18-24) nm by biologically synthesizeing to show more effectivity [45]. Size is an important factor to decide the destination and fate of the nanoparticles inside the body as differences in cytotoxicity could be correlated with different uptake rates [46].

Synthesis of nanocarriers:

Various researches over decades have focused on designing the nanocarriers mainly by two important approaches called top-down synthesis and bottom-up synthesis. Designed liposomal carriers, micelles, polymeric nanospheres, drug encapsulated hydrophobic polymer nanoparticles are few functionalities which are constructed by the "bottom up" synthesis category whose approach is based on self-assembly and emulsion systems [47 - 48]. Hueg developments and advancements have been made recently by introducing "top-down" approach in fabrication technology of micro and nano-fabrication system (MEMS & NEMS) using electromechanical approachs which have exhibited the potential for designing nanoparticles with precision in particle shape and size. Such type of approach could provide control over particle size, functionality and particle geometry with most accurate precision [49].

Their exist different ways and methods for synthesis of different nanoparticles such as fabrication by modification of the nano-precipitation method by homogenization and loading of chitosan nanoparticles by spray drying and in vitro cytostatic activity using silver nanoparticles synthesis, chitosan-stabilized selenium nanoparticles activity of synthesized silver nanoparticles from *Tinospora cordifolia* against multi drug resistant strains of *Pseudomonas aeruginosa*, biogenic synthesis of nanoparticles and its potential applications which are an eco-friendly approach to the synthesis of nanoparticles using *Euphorbia prostrata* extract that reveals a shift from apoptosis, green synthesis of copper-chitosan nanoparticles and synthesis of metallic nanoparticles by bacteria, fungi and plants. The evaluation synthesis of silver nanoparticles using *Phyllanthus amarus* and *Tinospora cordifolia* which are medicinal plants and also green synthesis of gold nanoparticles characterization by using plant essential oil menthapiperita, gene silencing by si-rna nanoparticles synthesized via sonochemical progress in the synthesis and surface modification of superparamagnetic iron oxide nanoparticles using silica [50 - 56]. Nanoparticles evaluation of in-vitro activity of silver nanoparticles synthesized using piper nigrum extract from silver nanoparticles biosynthesized using fruit juices, biosynthesis of silver nanoparticles from *Morinda tinctoria* leaf extract and their larvicidal activity against aedes *Aegypti Linnaeus*. This type of approach also tends to have the ability of resolving the limitation of bottom-up approach [57].

Bottom-up synthesis

This approach has been extensively studied and exploited in past to give rise to several types of potential nanocarriers which have been developed using this method for consideration, the polymeric nanoparticles, micelles, liposomes, nanoemulsions, dendrimers, biodegaradble and nonbiodegradable carriers, solid lipid nanoparticles, magnetic nanoparticles etc. Several invitro and invivo studies upon and using these nanocarriers have been done and are still going on [58]. Majority of these carriers are a sub category of colloidal systems which are governed by different molecular interactive forces like hydrophobic interactions, vander-walls forces, hydrogen bonding, and ionic interactions with exhibition of high polydispersity by such system such systems sometimes exhibit certain limitations such as in the functionalities of in-vivo drug release profiles, physicochemical characteristics, degradation kinetics of these carriers are difficult to evaluate and reproduce as they are variable [59].

Top-down synthesis:

Recent advancements and developments in design of the nanoparticles have made different nano imprint lithography processes possible under this category. Advance researches are being carried out in the field of nanofabrication for drug delivery using various top down construction processes such as soft lithography, thermal embossing, step and flash lithography, and UV embossing. These techniques have

already been explored at micron scale for synthesizing agents such as biocapsules. Previous studies have shown that microfluidic devices for fabrication of shape specific microparticles in case of nanofabrication, nanoimprint lithography, step and flash imprint lithography (S-FIL), particle replication in nonwetting templates (PRINT) have gained much attention [60 - 65].

CONCLUSION

We can conclude that the use of nanoparticles for the purpose of drug delivery to the cancer cells has significance as an intense value of upcoming novel method into the field of therapeutics and has a scope of grave and important developments that have capacity of changing the course of the treatment and therapeutic methodical history, the upcoming changes and development into the techniques targeted drug delivery system and the treatment properties of the nano particles itself has a scope of research findings involving targeted safe treatment methods and cure.

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