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Review Article

Nanomaterials Role in Lung Cancer Treatment: A Review

Rashmi Chandrayan [1]

[1] *Assistant professor, Dept. of physics JNCT, Bhopal, India*
rashmipancholi123@gmail.com

[*] *Corresponding Author:* rashmipancholi123@gmail.com
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Abstract: Nanotechnology encompasses the exploration, design, crafting, synthesis, production, and utilization of materials, devices, and systems on the nanoscale. "Nano" draws from the Greek term for dwarf, representing one billionth of a meter, or 109 m. Due to the prominence of particles within this scope, they possess distinct and enhanced attributes when compared to larger substances. Nanomaterials differentiate themselves from regular materials due to amplified surface area and quantum effects. Achieving targeted delivery of anti-cancer drugs to cancerous cells remains a challenge. Traditional therapy has inadequately addressed cancer due to drug accessibility, undesirable side effects, and drug resilience. Nanotechnology offers considerable potential for reshaping the way medical professionals diagnose and treat cancer patients. Nanotechnology has already made a substantial impact on patient care, presenting substantial future challenges, such as refining the architecture and engineering of cancer-targeting substances. Cancer, one of today's most devastating illnesses, claims millions of lives annually, propelled by uncontrolled apoptotic cell growth, requiring extensive procedures. Its clinical diversity and treatment resistance stem from genetic and phenotypic intricacies. In recent times, substantial efforts have been invested in developing nanotechnology to enhance and reduce the delivery of anticancer drugs to tumor tissue, as well as the distribution and toxicity of these treatments in healthy tissues. Significant advancements have occurred. Innovative nanotechnology platforms encompass polymer nanoparticles, liposomes, dendrimers, nanoshells, carbon nanotubes, superparamagnetic nanoparticles, and nucleic acid-based nanoparticles.
Lung cancer is a serious condition where abnormal cells grow uncontrollably in the lungs. It's often linked to smoking, but can also affect non-smokers due to various factors like genetics and environmental exposure. Treatment options include surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy. Early detection through screenings can improve prognosis. Quitting smoking and reducing exposure to pollutants are crucial preventive measures. Remember, each case is unique, so consulting with a healthcare professional is essential for accurate diagnosis and personalized treatment plans.
Crucial terms include "Nanotechnology," "Chemotherapy," "cancer," "Nanomaterials," and "Tumor."

Keywords: Nanotechnology, Chemotherapy, Nanomaterials, Anti-cancer drugs, Targeted delivery, Polymer nanoparticles, Liposomes .

1. INTRODUCTION

Nanotechnology involves studying, creating, producing, modifying, and using materials, tools, and systems at the nanoscale, which is one billionth of a meter or 10^(-9) meters. The term "nano" originates from the Greek word for "dwarf." Particles within this size range exhibit unique properties and behaviors, often superior to those of larger counterparts, due to factors like amplified surface area and quantum effects. These characteristics set nanomaterials apart from conventional materials[1].

Lung cancer is a prevalent and serious medical issue characterized by the uncontrolled growth of abnormal cells in the lung tissues. It is often linked to smoking, but can also affect non-smokers due to exposure to pollutants or genetic predisposition. This disease is categorized into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), each with distinct characteristics and treatment approaches.

Symptoms of lung cancer can be subtle, including persistent cough, chest pain, shortness of breath, and unintentional weight loss. Early detection is crucial for effective treatment, as lung cancer is frequently diagnosed at an advanced stage when the prognosis is less favorable.

Treatment options depend on the cancer's stage and type. They may include surgery, chemotherapy, radiation therapy, targeted therapies, and immunotherapy. However, lung cancer remains challenging to treat, often exhibiting resistance to therapies and a high likelihood of recurrence. Research efforts are ongoing to develop innovative treatments and improve patient outcomes.

Prevention is key, particularly for those at high risk due to smoking or exposure to carcinogens. Public health campaigns emphasizing smoking cessation and reducing environmental pollutants are essential in reducing lung cancer rates[2].

These two factors have the potential to enhance characteristics like reactivity, strength, electrical properties, and behavior within living organisms. The interpretation of nanomedicine slightly varies between the National Nanotech Initiative in the United States and the European Science Foundation and European Technology Platform. The former focuses on the nanoscale dimension, while the latter does not specifically emphasize it. As per the National Nanotech Initiative, nanotechnology involves understanding and manipulating matter at scales of about 1 to 100 nanometers, enabling novel applications. Nanomedicine is the application of nanotechnology in the medical field . However, the European Science Foundation describes nanotechnology as the utilization of molecular knowledge and tools related to the human body for diagnosing, treating, preventing, and improving health. In Europe, nanomedicine is defined as an application of nanotechnology to health, involving nanometer-scale materials with potential impacts on disease prevention, diagnosis, and treatment. The primary focus lies in drug delivery, diagnostics, regenerative medicine, and embedded devices, including imaging. Nanomedicines have the potential to revolutionize disease study, diagnosis, and treatment, spanning conditions from cancer to cardiovascular diseases to diabetes . Cancer stands as one of the most lethal diseases in today's world, claiming millions of lives annually. It involves the uncontrolled proliferation of apoptotic cells, which necessitates a complex and intricate process. Given its genetic and phenotypic complexity, cancer exhibits clinical diversity and resistance to treatment. Considerable efforts have been directed towards utilizing nanotechnology to improve the targeted delivery of anticancer drugs, minimizing distribution to healthy tissues and toxic effects . Innovative nanotechnology platforms have emerged, including polymers, nanoparticles, liposomes, dendrimers, nanoshells, carbon nanotubes, superparamagnetic nanoparticles, and nucleic acid-based nanoparticles[3] .

2. NANOTECH & NANOMETER NOTION

Nanotechnology involves the creation of practical materials, devices, and systems designed for manipulating substances. This field operates on an incredibly small scale, typically ranging between 1 and 100 nanometers. To put that into perspective, nanometers are a billionth of the width of a human hair, roughly 10 times larger than the diameter of a hydrogen atom. Notably, nanotechnology has been rapidly advancing in the realm of in vivo imaging and medical treatment. These developments hold significant promise for enhancing the care of cancer patients in the near future. Recent progress in the realm of nanoscale technology has given rise to a diverse array of innovative nanodevices, such as quantum dots, nanoshells, gold nanoparticles, and carbon nanotubes. These innovations are currently under extensive research[4].

2.1. REQUIREMENTS FOR NANOTECHNOLOGY/NANOMEDICINE IN CANCER TREATMENT

Nanoscale devices possess the ability to interact effectively with biomolecules both on cell surfaces and within cells due to their small size. This characteristic offers potential for disease detection and treatment by enabling access to various parts of the body. The technology holds promising suggestions for innovative cancer treatments[5]. This research delves into the emerging significance of these novel platforms in the realm of cancer diagnosis and therapy. Nanoparticles have been directed towards tumor sites using two strategies:

active targeting and passive targeting. Active targeting involves attaching specific ligands to tumor-focused nanoparticles. On the other hand, passive targeting leverages the size of nanoparticles and the distinct attributes of tumor vasculature. A central challenge in cancer treatment is the precise delivery of therapies to localized regions. Many anti-cancer drugs tend to exhibit partial selectivity towards cancer cells, posing risks of significant side effects and undesirable distribution to healthy organs and tissues. Consequently, the systemic administration of such drugs often leads to notable adverse reactions in non-targeted areas, imposing limitations on the permissible dosage of the drugs. Furthermore, rapid clearance and broad dissemination to non-targeted tissues necessitate higher therapeutic doses, which are frequently unfeasible due to cost and non-specific toxicity concerns. A key limitation of current cancer treatments is the cyclical pattern of escalated doses and associated toxicity. Patients are often reported to succumb to drug-related toxic effects sooner than the impact of tumor reduction[6].

NUMEROUS NANOTECHNOLOGYSYSTEMS ARE AVAILABLE FOR THE PURPOSE OF CANCER TREATMENT.

Polymeric nanoparticles (NPs), liposomes, dendrimers, nanoshells, carbon nanotubes, and superparamagnetic nanoparticles (NPs) represent several frequently utilized nanotechnology frameworks for addressing cancer therapeutics. These nanotechnology platforms exhibit enhanced capability to infiltrate tumor blood vessels due to their compact dimensions and varied structural and physicochemical features, such as enhanced permeability and retention (EPR) effects. Additionally, cancer-targeted components like antibodies, ligands, and lectins can be employed for the specific targeting of tumor cells.

3. NANOTUBESCOMPOSED OF CARBON

Carbon nanotubes represent a molecular structure composed of carbon, initially identified in the latter part of the 1980s . Numerous sectors find significant fascination in the utility of carbon nanotubes, attributing to their remarkable characteristics: they boast a strength 100 times that of steel while being merely one-sixth its weight, coupled with exceptional thermal traits and conductivity . Analogous to the previously discussed nanoshells, carbon nanotubes have predominantly found application in the delivery of DNA payloads to cellular environments and in the treatment of cancer through thermal ablation therapy .

4. NANOSTRUCTURES WITH SHELL-LIKE PROPERTIES

Polymeric nanostructures with shell-like characteristics (measuring 20–60 nm) originating from D-block copolymers can be methodically fabricated layer upon layer, following a process of NPS self-assembly involving oppositely charged polymers. This results in the formation of a core/shell structure . Notably advantageous are nanoshells with a core comprised of silica, possessing a diameter of 120 nm, and encompassed by a gold shell measuring 10 nm. The exceptional benefit here arises from their aptitude to absorb near-infrared (NIR) light at 800 nm, which in turn generates substantial and lethal heat, detrimental to cells. An added advantage lies in the fact that NIR light is capable of penetrating human tissue to significant depths, as tissue chromophores exhibit minimal energy absorption within the NIR spectrum, thus evading harm. The utilization of nanoshells brings forth a valuable aspect,

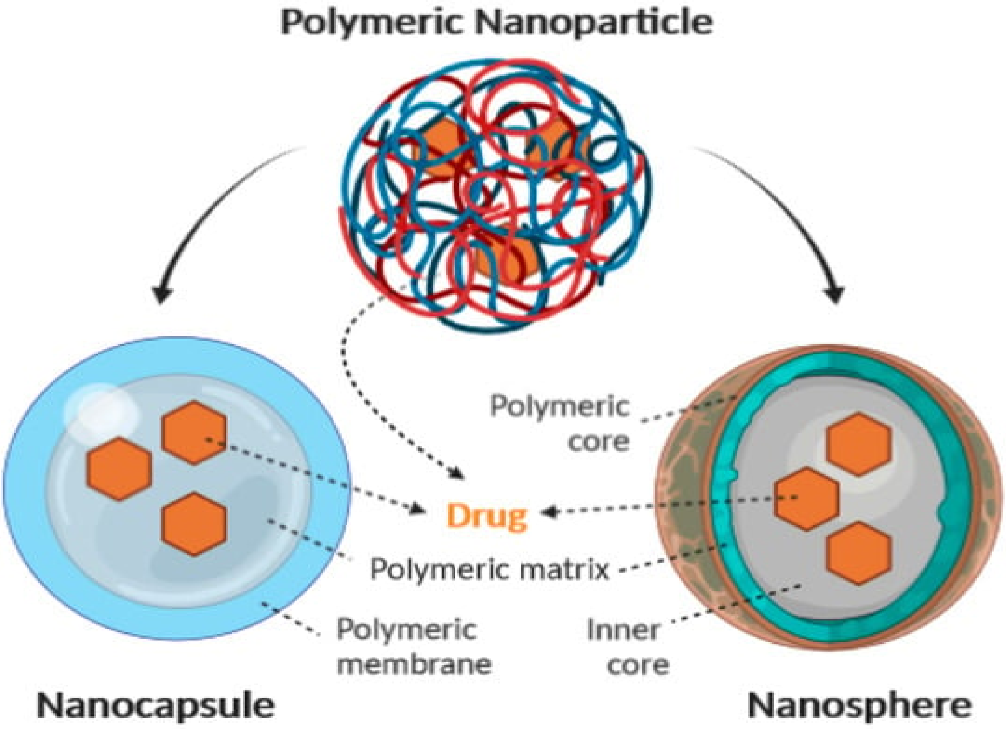
One notable aspect of this approach is that the energy can traverse through intact tissue, sparing adjacent cells from harm, and exclusively eradicating tumor cells singled out by the nanoshells[7].

5. DENDRITIC STRUCTURES

Dendritic architectures, characterized by their intricately branched structure, have garnered extensive exploration as intricate molecules with uniformly distributed complexity. The unique interplay of a hydrophobic core and a hydrophilic surface in dendritic structures enables the transportation of both hydrophobic and hydrophilic medications. Factors such as the generation number, core and branch composition, as well as surface functional groups, collectively influence the dimensions, configuration, and pharmacokinetics of dendrimers. The alteration of dendrimer pharmacokinetics and biodistribution can also be significantly achieved through chemical modification. Dendrimers find versatile applications encompassing solubility enhancement, photodynamic therapy, drug delivery, bioimaging, cancer therapy, and the construction of 3D nanoscale coreshell arrangements. Concurrently, multivalent dendrimers engage with numerous targets in drug development. Characterized by their spherical nature, dendrimers typically exhibit a diameter less than 5 nm. Their primary beneficial trait is the proliferation of polymer branches, creating an extensive surface area to which therapeutic agents and target molecules can be affixed. The inception of a typical dendrimer entails an ammonia (NH_3) core that initiates the reaction with acrylic acid, leading to the formation of triacid molecules[8].

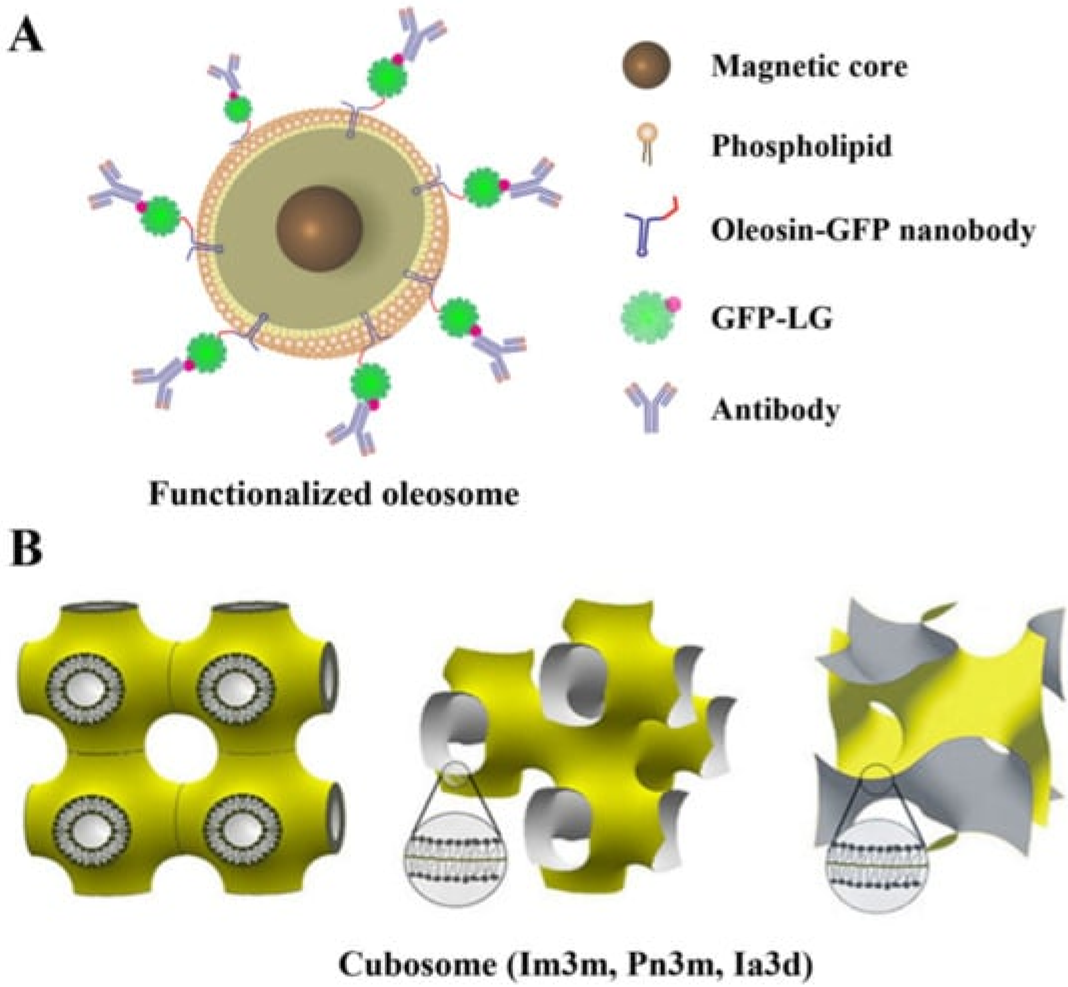
Polymeric nanoparticles are minute particles made of polymers

Polymer nanoparticles can be created from natural or synthetic polymers for drug delivery. These nanoparticles, made from biodegradable or nonbiodegradable polymers, have been effective in targeted anti-cancer medication delivery. Polymer nanoparticles, a successful nanotechnology platform, are versatile in administering anticancer drugs. They can transport low molecular weight drugs and larger molecules like genes and proteins. Examples include Poly (D, lactide coglycolide) nanoparticles, potent protease inhibitors, and cytokeratin-specific systems. Monoclonal antibodies have also been utilized to counter excessive proteolysis, reducing the risk of metastasis in breast tumor cells. Stabilizing nanoparticle surfaces and achieving active targeting often involve hydrophilic polymer binding, grafting, or adsorption, such as with polyethylene glycol (PEG). By regulating copolymers and using folic acid conjugation, the stability of self-assembly in aqueous media can be enhanced, along with improved in vivo tumor site selectivity via ring-opening metathesis polymerization[9].



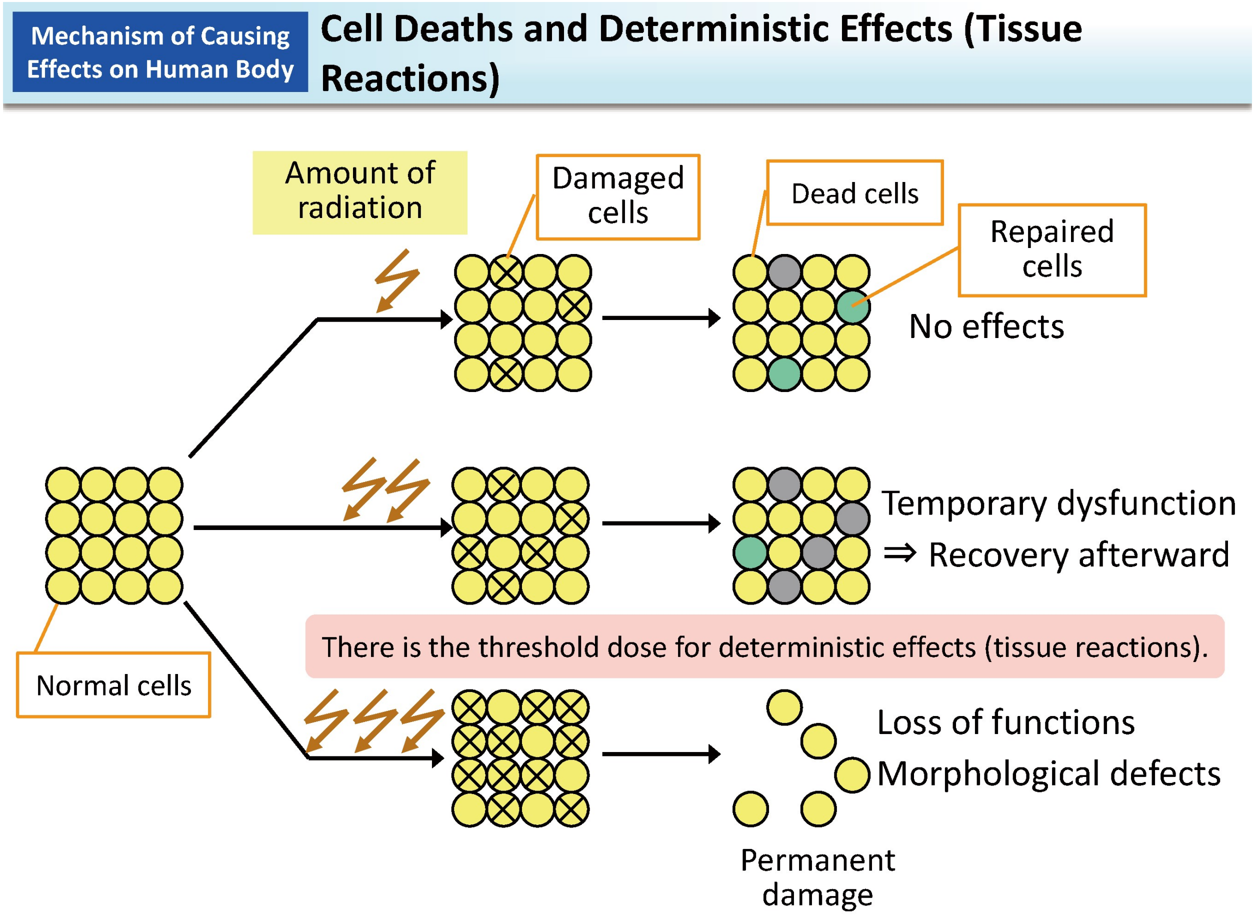
6. LIPOSOMES

Liposomes are closed vesicles with a lipid bilayer that holds an aqueous compartment for drug encapsulation. Despite their size (90-150 nm) slightly exceeding the conventional limit (≤100 nm), liposomes are not new in nanotechnology but remain a key focus of nanotech research. Through hydrophobic interaction, they form lipid bilayers and are excellent for delivering both hydrophobic and hydrophilic drugs, notably showing prolonged blood circulation for efficient targeting. Lipids with varying properties enable the creation of temperature or pH-sensitive liposomes. In a study, we assessed the effectiveness of 1-methylxanthine (1MTX) as a radiosensitizer and the in vivo impact of temperature-sensitive liposome 1-methylxanthine (tslMTX) with hyperthermia and radiation. Injecting MTX inhibited tumor growth in a mouse model, while tslMTX combined with hyperthermia and radiation suppressed tumor growth. To target leukemic cells, pH-sensitive immunoliposomes (ILs) with NIPAM in the bilayer were bound to anti-CD33 antibodies. pH-sensitive ILsCD33 immunoliposomes showed high cytotoxicity to HL60 cells, suggesting potential for acute myeloid leukemia treatment. FDA-approved liposomes include liposome-encapsulated doxorubicin, displaying potent antitumor activity across cancer types[10].



7. Innovative Cancer Treatment

The rising trend is towards cancer treatment that specifically targets malignant cells without harming healthy ones. Nanotechnology has introduced more accurate materials and methods for cancer therapy. Modern cancer treatment approaches leveraging nanotechnology, like photodynamic therapy (PDT), irradiation, radiofrequency therapy, and diagnostics, enable innovative and minimally invasive cancer treatment strategies that were previously absent (Fig. 2). With these emerging technologies, it's possible to pinpoint cancer cells while sparing healthy ones. Consequently, cancer cells are eliminated while normal cells survive[11].



APPLICATION OF NANOTECHNOLOGY IN GENE THERAPY

The foundation of gene therapy lies in the notion that certain external genes can be inserted into the genetic makeup of cancerous cells to induce a tumor-suppressing impact. This domain constitutes one of the rapidly advancing fields in both preclinical and clinical exploration of cancer. Conventionally, viral vectors have been the primary agents for introducing genes to target cells, but they come with considerable risks of evoking immune and inflammatory responses within the host. Challenges tied to viral vectors encompass issues of toxicity, immune and inflammatory reactions, genetic control, and precision targeting. Furthermore, there is an ever-present risk of viral resurgence and infection. To surmount these challenges, substantial interest revolves around non-viral means of gene transfer technology. A non-viral vector offers the advantage of being non-toxic and cost-efficient, with a diminished immune response likelihood[12] .

Prominent among the non-viral vectors are liposomal-mediated cationic polymers and nanoparticles. The efficacy of a non-viral gene delivery agent hinges on its physical attributes such as nanoparticle size, shape, charge density, and colloidal stability. Jere and colleagues achieved successful delivery of a biodegradable nanopolymer carrier loaded with small interfering Akt1 RNA to cancer cells. This intervention led to the suppression of Akt1 protein, resulting in diminished cancer cell viability, proliferation, malignancy, and metastasis.

RADIOFREQUENCY TREATMENT AND NANOTECHNOLOGY-ENHANCED RADIOTHERAPY

Enhanced radiation dosages utilizing materials with high atomic numbers (Z) have been a longstanding area of interest. Research has indicated that introducing a high Z material into a tumor leads to greater photoelectric absorption within the tumor compared to the surrounding tissue, potentially amplifying radiation therapy's dose impact on the tumor. For practical clinical application, substances that enhance radiation's effect should considerably improve the therapeutic ratio, be easily accessible, user-friendly, and non-harmful. Gold (Au; Z = 79) or nanogold (gold nanoparticles) have demonstrated dose-amplifying effects in cellular experiments and mouse models[13]. Gold nanoparticles have been extensively explored across biomedical applications due to their compatibility with living systems and their ability to bind with biomolecules. An inquiry into the enhanced dose effect and the lethality of gold nanoparticles coupled with a single-dose electron beam was conducted in B16F10 melanoma-bearing mice. Although radiofrequency ablation has found use in treating cancer, cardiac conduction anomalies, and nerve damage, it is most prevalent in cancer therapies.

The primary application of radiofrequency ablation is for unresectable malignant liver damage. While the traditional method involves inserting probes into tumors, nanotechnology allows the development of non-invasive radiofrequency ablation techniques. Both lab-based and live subject investigations have unveiled that gold nanoparticles enhance cancer cell demise within non-invasive radiofrequency fields. Gold nanoparticles might offer a targeted approach to cancer cell destruction. Utilizing pioneering non-invasive radiofrequency equipment and gold nanoparticle-amplified solutions, both tissue and cancer cells' heating have been achieved in vitro and in vivo[14].

Gene therapy involves directly delivering and expressing DNA into affected cells for therapeutic purposes. To achieve this, nucleic acid-based nanoparticles are utilized, where the chlorotoxin peptide (CTX) is attached to DNA-complexed polyethyleneimine (PEI) in the nanoparticles. Subsequently, these nanoparticles are functionalized with Alexa-Fluor 647, a near-infrared molecule, resulting in a neutral nanocarrier ligand matrix . Both in vitro and in vivo experiments have confirmed the successful gene delivery to colon and liver cancer cells using mixed nanoparticles containing 4th generation poly(amidoamine) (PAMAM) dendrimers and plasmid DNA. RNAi and ASO therapies utilize oligonucleotides to hinder the expression of specific target genes, aiming to treat the underlying diseases. The development of RNA nanoparticles began with the use of Poly(propylene imine) (PPI) dendrimers.

8. UTILIZING NANOTECHNOLOGY FOR SYNERGISTIC THERAPIES

Resistance to chemotherapy presents a significant clinical challenge that hampers the efficacy of cancer drug treatments. Owing to the selective pressure of the tumor microenvironment, cancer cells can trigger multidrug resistance (MDR). Cancer cell MDR involves their capacity to counteract drugs that are functionally and structurally distinct. Mechanisms of MDR encompass sequencing, heightened drug efflux, diminished drug influx, modified binding sites, activation of detoxifying enzymes, obstruction of apoptotic signaling, and DNA mending. To surmount MDR, the utilization of nanotechnology for combined therapies has garnered growing interest in recent times. The strategy involves merging diverse modifications (e.g., regulation of drug efflux, apoptotic threshold, and intracellular pH) and energy-based treatments (e.g., ultrasound, hyperthermia, and photodynamic therapy) that exhibit significant potential in enhancing the management of cancers resistant to multiple drugs[15].

8.1. OBSTACLES OF NANOTECHNOLOGY IN CANCER TREATMENT

Nanotechnology offers numerous benefits in the realm of cancer treatment. Thanks to its small size, the nanotechnology platform can infiltrate the tumor's blood vessels using the EPR effect. Moreover, the attachment of hydrophilic polymers/oligomers can extend the duration of exposure of tumor tissue to antineoplastic agents, leading to longer cyclic half-lives. Meanwhile, the incorporation of tissue-specific residues like antibodies, lectins, and cancer cell-specific ligands can aid in achieving precise targeting of tumor cells through nanotechnology platforms. Addressing the significant hurdle of cancer cell MDR, which renders cancer therapies ineffective, has been tackled by developing multifunctional nanotechnology platforms in combination with other therapies, yielding noteworthy success.

Nonetheless, the advancement and practical application of nanotechnology platforms in cancer treatment continue to confront various obstacles. These encompass limited understanding of cancer cell physiology, the varied and suboptimal functional capabilities of medical nanomaterials, as well as the absence of standardized clinical evaluation criteria. However, propelled by the latest strides in functionalization rooted in an in-depth comprehension of cancer cell physiology, nanotechnology platforms hold the potential to revolutionize cancer treatment. This could usher in uncomplicated and efficient targeted therapeutic approaches[16].

9. CONCLUSION

Administering anti-cancer drugs specifically to cancer cells remains a significant hurdle due to drug limitations, undesirable side effects, and drug resistance. Nanotechnology offers substantial potential in revolutionizing current approaches to diagnosing and treating various cancer types in patients. The impact of nanotechnology on patient treatment is already emerging as a notable development, presenting key challenges for the future, such as refining the design and engineering of materials that target cancer.

To harness the capabilities of nanoparticle techniques, a deeper comprehension of factors influencing the targeted delivery of nanomaterials to cancer sites is necessary, encompassing tumor-specific, tumor-site, and host-specific influences. Numerous nanoparticle systems are under

investigation to enhance the precision of delivering potent chemotherapeutic agents, aided by their optimal size and surface characteristics, enabling attachment to bioactive molecules.
Clinical utilization of liposomal and protein-based nanomedicine formulations is already in progress, while various novel formulations are undergoing phase 2 and phase 3 assessments. The future landscape of nanomedicine is poised to introduce inventive platforms for cancer treatment, and the insights provided in this research have the potential to enhance the overall efficacy of cancer treatment involving nanoparticle strategies.

CONFLICTS OF INTEREST

There are no conflicts of interest and disclosures regarding the manuscript.

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