Nanoparticle-Based Drug Delivery Systems for Tumor Treatment: Advancing Solutions to Overcome Drug Resistance

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Abstract: The potential of nanoparticles (NPs) as a drug delivery mechanism (DDM) has prompted extensive study and use of nanotechnology in tumor cell (TC) treatment. Compared to conventional medications, NP-based DDM offers greater stability and biocompatibility, enhanced absorption and preservation, and focused accuracy, which are some of its unique advantages. This drug-carrying technology has reached a new level with the use and improvement of composite nanoparticles (NPs), which combine the unique characteristics of multiple NPs. Additionally, NP-based DDMs have demonstrated effectiveness in overcoming cancer-related drug resistance (DR). Improving medical translation must address limited dose capacity, stability limitations, and potential harmful effects. Researchers are exploring ways to enhance DDM, including the development of novel drug-encapsulating techniques and modifications to NP surfaces. Potentially huge gains in treatment efficacy may result from optimizing medication integration in such systems. One obstacle to medical translation is stability issues. Applying protective covers and improving formulations are two methods that researchers are exploring to extend the lifespan of NPs.

Additionally, before progressing with clinical trials, efforts are being made to minimize the likelihood of negative side effects by carefully selecting compounds that are biologically compatible for NP synthesis and conducting comprehensive toxicity evaluations. Following that, we continue with the innovation of nanoparticle design and functionalization; these types of delivery systems are poised to play a key role in various areas of next-generation tumour therapies. Which provides various offers through robust pathways to overcoming drug resistance, accelerating clinical translation.

Keywords: Nanotechnology, Drug Delivery, Nanoparticles, Targeted precision, Drug resistance.

1. INTRODUCTION

Cancer ranks as the second foremost cause of mortality worldwide. The most recent data from the WHO indicates that in 2024, there were approximately 11.12 million cancer-related deaths and 20.08 million additional cases recorded. Chemotherapy is among the most therapeutically accessible treatments for combating cancer [1]. A significant amount of effort has been dedicated to researching chemotherapy drugs. (Sharma *et al*., 2021) Cisplatin or Anticancer drugs are regarded as the primary medication for solid tumors and lung cancer. Anti-cancer drug is used in the treatment of solid tumours, often to address various challenges due to drug resistance, with alternative delivery strategies including a nanoparticle-based. NP-based agents constitute fifty percent of the current utilization of chemotherapeutic medications.

Nevertheless, despite its essential function in cancer therapy, various limitations have considerably constrained the clinical efficacy of anticancer drugs in therapies for cancer. The low selectivity of chemotherapy drugs for cancer results in heightened adverse reactions in patients [2]. The anticancer efficacy of these drugs is facilitated through nonspecific adherence to genomic DNA. DNA damage through this mechanism results in significant death and necrosis in both cancerous and normal cells. As a result, significant adverse effects, such as kidney damage, emesis, and brain damage, commonly manifest in patients receiving cisplatin-based chemotherapy.

Moreover, DR may develop following multiple cycles of chemotherapy, resulting in unsuccessful treatment. DR cancer, marked by diminished drug absorption, deactivation of drug through protein binding, or the emergence of alternate survival mechanisms, leads to ineffective suppression and subsequent tumor resurgence [3]. Consequently, the amalgamation of platinum-based drugs with additional chemotherapy drugs has emerged as an efficacious strategy for cancer treatment. Nonetheless, mixed therapy encounters additional problems in patients and challenges in treatment design.

The primary objective of this research is to develop and evaluate advanced types of nanoparticles, followed by a drug delivery system, which effectively overcomes multidrug resistance in tumour cells. To enhance targeting, drug accumulation, cellular uptake, and the tumor microenvironment. This research primarily focused on addressing the key resistance factors, including drug efflux, drug deactivation, and tumor heterogeneity.

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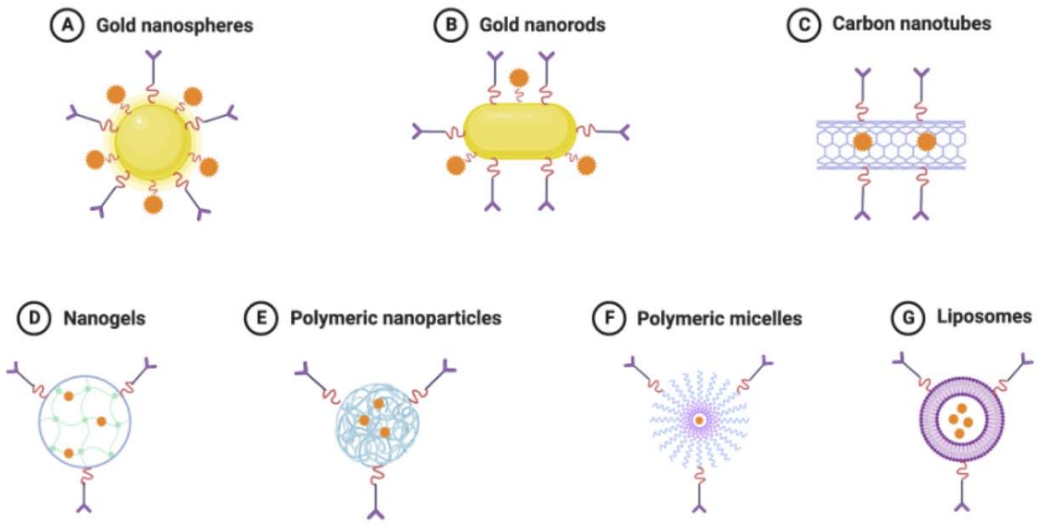

Figure 1: Different kinds of NPs have been utilized in cancer therapy [4].

As shown in Figure **1**, various types of NPs have been utilized to treat cancer. NPs may be able to enhance the effectiveness of chemotherapy drugs while reducing their side effects by targeting TC [4]. In addition, they might be able to ablate thermally, which means they can heat TC to the point of death. NPs may also be able to improve imaging techniques used in healthcare, which could help detect and monitor tumors more effectively.

Nurse practitioners have significant potential to improve healthcare and advance cancer research. Because of this, it is crucial to thoroughly examine these traits and understand their impact on NP behavior before proceeding to human studies [5]. We need to find ways to make NPs last longer and keep them from sticking together in organs if we want to use them for therapeutic purposes. This study provides us with more information about the NP-based DDM as a potential treatment option for cancer.

1.1. Role of Nanoparticles in Overcoming Drug Resistance

Nanoparticles play a crucial role in overcoming drug resistance and enhancing drug accumulation in tumor cells, thereby bypassing efflux mechanisms. Consider that liposomal doxorubicin is used to improve the delivery of doxorubicin and reduce cardiotoxicity in resistant tumors [14].

2. THE CONSEQUENCE OF DDM AND ITS USAGE IN NANOMEDICINE

NP-based DDM, developed over the past four decades, concentrate on evaluation and therapy, emphasizing the reversal of DR, lowering of harmful reactions, and enhancement of the drugs' chemical and physical characteristics. NP-based medicines and pharmacologic regulators of DR processes can be incorporated into NP via physical encapsulation, covalent attachment, and electrostatic interaction, enhancing pharmaceutical stability, aqueous solubility, and receptor selectivity [6-7].

Furthermore, the enhanced permeation and persistence effect constitutes a viable strategy for NP-based DDM. The enhanced permeability and retention effect, an inherent physical phenomenon, facilitates the indirect administration of TC, resulting in NP aggregation at the TC location that is 15 to 55 times greater than in healthy tissue [8]. Moreover, NPs typically infiltrate cells via endocytosis (a process of cellular uptake) at a gradual transport rate. Nevertheless, a NP possesses a substantial drug payload and circumvents the limitations of cellular membrane carriers.

They may also be able to cross the blood-brain barrier, which allows therapeutic drugs to reach the brain directly and help people with neurological diseases like Alzheimer's. By making chemotherapy more effective while minimizing its adverse effects on the body, this personalized DDM could significantly alter the way cancer is treated. Author (Mahmood *et al*., 2022) Engineered nanoparticles can also release drugs in a controlled way, ensuring the therapeutic effect lasts for a long time. One problem with using NPs to deliver drugs to specific areas is that TC might become resistant to treatment [9]. Long-term use of NP-delivered chemotherapeutic drugs may become less effective at treating cancer if TC adapts and becomes resistant.

Despite the potential benefits of DDM, the development of DR in TC could render NPs less useful in cancer therapy. The DR issue highlights the importance of continued study and improvement in targeted DD. Scientists are working hard to find answers to DR. For example, they are making new DDM and combining several NPs. This obstacle may prevent us from utilizing NPs to their full potential in targeted DDM, which could lead to improved cancer treatments for patients [10].

3. NP-ASSISTED DDM

There is a possibility that NP-based DDMs could enhance cancer treatment by minimizing harm to living tissues while also addressing TC [11]. It is still necessary to fix DR before these systems can fulfill their promises. Researchers are looking at several ways to make these systems work better and stop DR. By giving more than one drug at the same time using NP-based DDM, the goal of combination therapy is to target many pathways and causes of DR. By getting around DR in TC, NP may be able to reach its targets and have its therapeutic effects. Controlled administration of medications by NPs could reduce side effects while maintaining the same dosage of medication.

To further improve their ability to target TC while sparing healthy tissues, researchers are working to make NP-based DDM more selective. This holds great promise for developing future cancer treatments that are more effective and tailored to the patient's needs [12]. Cancer cell DR reversal or reduction gene therapy medications are now the subject of active investigation.

NPs can potentially encapsulate chemotherapeutic drugs, specifically targeting TC and evading treatment-inhibiting resistance mechanisms. These NPs may deliver drugs directly to TC to overcome DR and improve treatment effectiveness. However, since mutations or genetic variations may reduce TC's sensitivity to the effects of NPs, not all TCs may show uniform sensitivity to NP-based treatments.

Some TCs may find ways to remove or destroy NPs actively, which would make them useless for delivering drugs to those cells. Through their complex interaction, nanoparticles and TC may cause harmful or unexpected effects, which could risk healthy organs and tissues. NP-based treatments may work differently on different kinds of TC [13]. There may be factors associated with certain cancers that make them less likely to respond to NP therapies.

Before using NP-based treatments on a large scale in healthcare settings, it is essential to carefully consider the risks of side effects and other potential problems that may occur. Another important consideration is how to transport NPs to TC. The effectiveness of NPs depends on how well they can reach and enter the tumor. To protect patients and minimize unexpected risks, understanding the potential long-term effects and safety features of NP-based medicines is crucial.

4. METHODS OF TARGETING

For DDM, the ability of NP carriers to selectively target TC is crucial for enhancing treatment efficacy while minimizing harm to healthy cells. The specific design of NP-based drugs has been the subject of much study. To effectively tackle the issues of targeting cancer and developing nano-carrier systems, it is essential to comprehend cancer biology and the interactions between nano-capsules and TC. The targeting techniques may be classified into two main groups: passive targets (PT) and active targets (AT), as shown in Figure **2**.

4.1. PT

PT aims to use the distinct properties of cancer and normal tissues. In PT, the medications are effectively administered to the target spot to fulfill a therapeutic function. The significant growth of cancerous cells stimulates coagulation, and numerous holes in the vascular wall result in diminished selectivity of tumor arteries relative to healthy vessels. Accelerated and aberrant vasculature facilitates the extravasation of macromolecules, including nanoparticles (NPs), from the blood arteries supplying the tumor, leading to their accumulation within the cancerous tissue.

Concurrently, the impaired lymphatic circulation linked to cancer enhances the accumulation of NPs, facilitating the delivery of their payloads to TC. These activities induce the enhanced permeability and retention (EPR) effect, a major mechanism of PT. The dimensions of NPs influence the EPR effect, as several studies have demonstrated that smaller NPs exhibit superior penetration but do not extravasate into regular arteries. Larger fragments are more prone to elimination by the body's immune response.

Alongside the impact of EPR, the cancer ecosystem has a significant influence on the indirect transmission of nanomedicines. The breakdown of glucose is a physiological hallmark of TC and serves as the primary

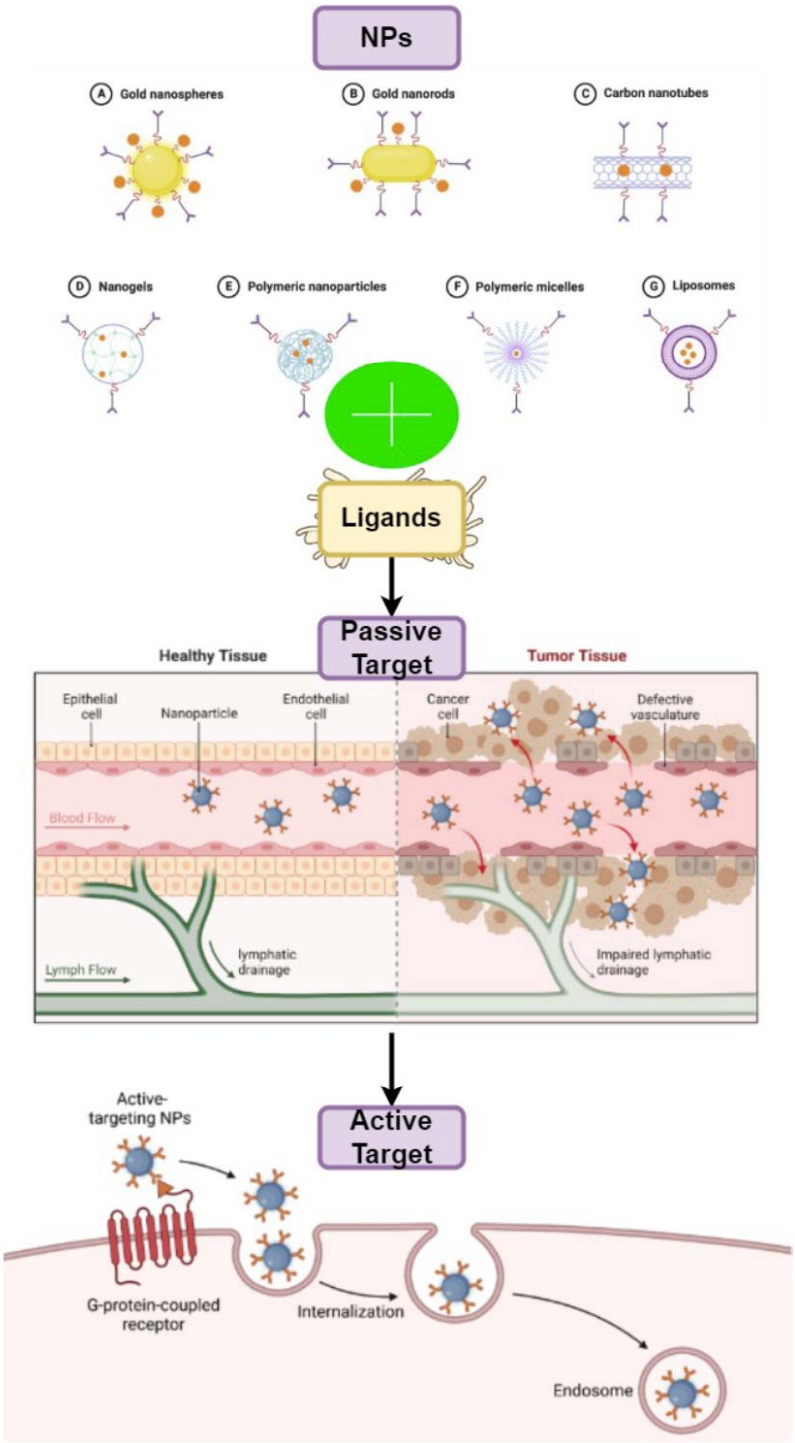

Figure 2: PT and AT of NPs to TC [4].

energy source for their growth. It produces a highly acidic atmosphere, decreasing the pH of the cancer microenvironment. Consequently, some pH-sensitive NPs are activated by reduced pH values and may release medications near the target cell (TC). Nonetheless, PT has several disadvantages, including general DD, the local presence of the EPR effect, and varying susceptibility of blood vessels across different cancers.

4.2. AT

AT precisely identifies TC by immediate connections between drugs and sensors. The ligands on the exterior of nanoparticles are chosen to concentrate on enzymes elevated on TC surfaces, enabling the differentiation of cells targeted from normal cells. The engagement of compounds on NPs with targets on TC surfaces triggers endocytosis via

receptors, facilitating the effective discharge of therapeutic medicines from ingested NPs. Consequently, AT is especially appropriate for the DDM of macromolecular drugs, including peptides and siRNAs. The categories of target components are monoclonal antigens, amino acids, proteins, minerals, and sugars. These molecules selectively attach to receptors on particular cells.

5. METHODS OF NPS IN COMBATING DR

DR remains a significant challenge in the fight against cancer, regardless of the proliferation of cancer therapeutic modalities. DR results in the ineffectiveness of several cancer therapies, contributing to disease advancement and unfavorable outcomes. Tumor DR processes comprise cellular and pharmacological variables, including the amplification of ATP-binding cassette (ABC) transporter genes, impaired apoptotic pathways, blood vessel pressure, and an acidic, hypoxic cancer microenvironment. Nanotechnology used in DDM for tumor therapy has substantially impacted mitigating DR.

Efflux transporters (ET) are a subset of ABC receptors critical in mediating DR, as shown in Figure **3**. ET diminishes interstitial levels of drugs by expelling the drug from the cell, resulting in unsuccessful therapy. P-glycoprotein (P-gp), an extensively studied ET, is elevated in various DR cancers. Moreover, elevated levels of P-gp have been correlated with suboptimal therapy response in several malignancies, including breast and ovarian cancers. A multitude of studies has shown that certain chemotherapeutic-loaded NPs can evade the ingestion of chemotherapy drugs by ET, as NPs predominantly enter cells via endocytosis rather than diffusion and discharge the medication at a perinuclear location within the cell, distant from the cell walls and efflux pumps. The NP-based DDM may alter the regulation of the release of drugs.

Integrated therapy (IT) is an alternative approach for the treatment of DR malignancies. Consequently, NP-based IT has effectively addressed the biophysical discrepancies among various medications by integrating several medicinal products into a singular drug carrier, hence combating DR and enhancing the efficacy of cancer treatment. Besides circumventing ET, another strategy to address DR mediated by these transporters is to reduce their production and activity. This method may be accomplished by formulating nanoparticles that incorporate efflux pumping blockers and chemotherapy treatments or by diminishing the ATP available to efflux pumping.

Malfunctioning apoptotic mechanisms (AM) enable TC to evade apoptosis and enhance survival, thereby facilitating disease resistance (DR) in cancer. The impaired apoptosis mechanism (AM) is often initiated by the dysregulation of Bcl-2 and the transcription factor nuclear factor kappa B (NF-κB). Bcl-2 is an

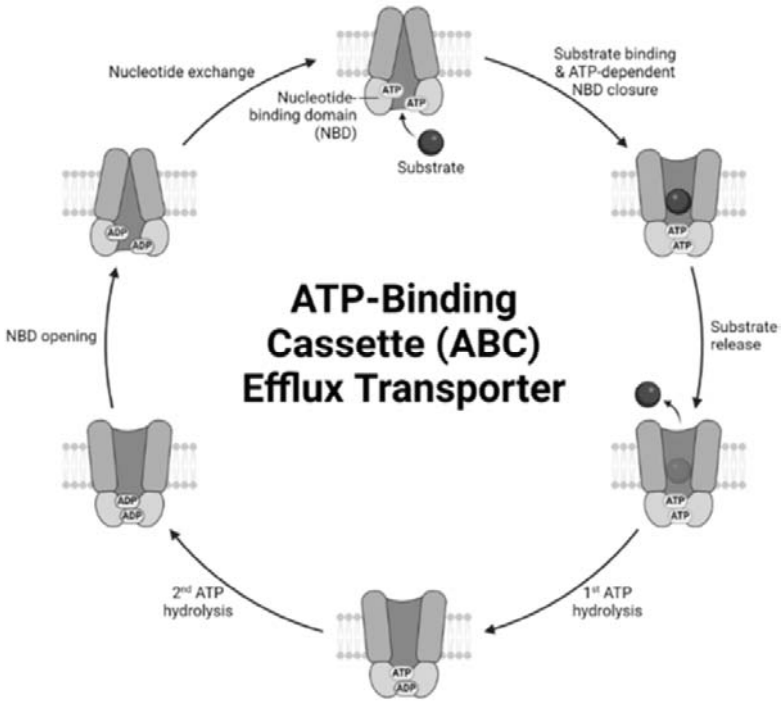

Figure 3: ABC ET [4].

extensively studied anti-apoptotic amino acid, prominently expressed in several malignancies. It plays a crucial role in DR, indicating the possibility of it as a target for overcoming DR. Increasing data suggests that the combined administration of Bcl-2-targeted siRNA and chemotherapy drugs using NPs is a viable strategy to combat DR in cancer. NF-kB inhibitors, such as curcumin, have also been employed in NP-based integrated treatment.

Alongside inhibiting anti-apoptotic factors, pro-AM stimulation may also address AM-mediated DR. Integrating ceramide with the chemotherapy agent docetaxel enhances the therapeutic effectiveness in many DR cancer models. Recent research has indicated that ceramide can reinstate the production of wild-type p53 protein, a crucial tumor inhibitor, by influencing the alternative splicing of pre-mRNA. In this procedure, NPs provide a more efficient mechanism for delivering ceramide into TC with p53 missense deletions that are a significant oncological occurrence. Given p53's critical involvement in apoptosis, restoring p53 activity or other suppressor genes is a viable strategy to counteract DR in cancer. Consequently, p53 genetic therapy using an NP-based DDM has undergone more investigation. The transfection of the p53 gene using cationic solid lipid nanoparticles and Polylactic-co-glycolic acid has been demonstrated in lung and breast cancer cells, respectively. The findings demonstrate the successful stimulation of apoptosis and suppression of tumor development.

To interpret Table **1** describes about summarize the various types, materials, advantagesa and clinical status of nano[article drug.

6. CHALLENGES IN NP-BASED DDM FOR CANCER TREATMENT

Immunologic therapies that utilize the body's immune system to identify and eliminate TC have transformed cancer therapy. Nonetheless, it is essential to comprehend how these medications could influence the likelihood of acquiring cancer. Scholars aim to enhance treatment options and ensure patient safety by investigating the long-term effects of antibodies and their impact on tumor risk indicators.

The antibodies may elevate the risk of developing tumors. This means it suppresses the immune system and promotes tumor development, as well as impairs natural tumor mechanisms. Healthcare providers can offer more personalized care and better educate patients when they understand how immune treatments affect tumor risk factors. Furthermore, if we can identify potential connections between the dangers of cancer and treatment, it may be easier to develop methods to reduce risks and improve patient outcomes.

One part of a comprehensive study could involve looking into the long-term effects of a specific chemotherapy drug on the risk factors for cancer in a group of patients who have cancer. The experiment will

Table 1: Summary for Types, Materials, Advantages, Clinical Status and Nanoparticle Drug

Nanoparticle Type	Core Materials	Key Advantages	Clinical Status	Example Drugs
Liposomes	Phospholipids, cholesterol	Enhanced biocompatibility, less toxicity, and high drug loading	FDA-approved	Doxil (Doxorubicin), DaunoXome
Polymeric Nanoparticles	PLGA, PEG-PLA, chitosan	Consistent release, adaptable shape, and precision targeting	Experimental / Clinical Trials	Paclitaxel-loaded NPs
Solid Lipid Nanoparticles (SLNs)	Glyceryl monostearate, triglycerides	Physical stability is high, allowing for scalable production.	Experimental	Curcumin SLNs
Gold Nanoparticles (AuNPs)	Gold core, thiol-functionalization	Simple surface alteration with photothermal treatment	Pre-clinical / Phase I-II trials	TNF-AuNP conjugates
Mesoporous Silica Nanoparticles (MSNs)	Silica, surface-functionalized	Precise control of pore size and high surface area for loading several drugs	Experimental	Doxorubicin-MSNP systems
Dendrimers	PAMAM, PPI polymers	Targeting with pinpoint accuracy and a multivalent surface	Experimental	Methotrexate–dendrimer complexes
Carbon-based Nanoparticles (e.g., CNTs, Graphene Oxide)	Carbon nanotubes, graphene	Superior medication loading, photothermal, and photodynamic capabilities	Pre-clinical	DOX–CNT conjugates
Micelles	PEG-PCL, PEG-PLA copolymers	Dilute hydrophobic medications for enhanced photodynamic therapy (EPR)	Some FDA-approved	Genexol-PM (Paclitaxel micelle)

take place over several years. It will compare patients who received chemotherapy to a control group that did not receive the treatment, and it will look for any changes in the patient's risk factors.

Patients who received immunotherapy as part of their treatment may provide a clear counterexample by demonstrating a decrease in risk markers rather than an increase. Changes in diet and exercise, variations in genetic makeup, and adverse drug reactions are all possible causes. Before making any definitive statements about the drug's impact on cancer risk factors, researchers need to consider these uncertainties.

The issue with this as a nanoparticle-based drug delivery system is that it provides various strategies, which are, however, followed by easy-to-overcome limitations in clinical translation. This includes the limited tumor penetration with dense extracellular matrix, rapid clearance within the phagocyte system.

Success in animal models uses a nanoparticle drug delivery system, which means that translating to humans often differs in the tumor biology, immune response, and nanoparticle behaviors.

Researchers need further trials to identify why immunotherapy reduces patient risk factors. By looking at potential changes to one's way of life, genetic makeup variations, and treatment response, one may learn everything there is to know about the drug's effect on cancer risk factors. The results and recommendations for chemotherapy treatment will be more accurate.

A major roadblock in the delivery of cancer nanodrugs is the immune system's ability to either eliminate NPs or accumulate them in the wrong tissues, reducing their effectiveness. The tumor's environment, with its dense cell matrix and twisted blood vessels, makes it difficult for nano drugs to permeate and distribute throughout the tumor [14]. The engineering of customized DDM involves attaching specific ligands to the surfaces of NPs to overcome these obstacles; these ligands then bind to the receptors found on TC (Figure **4**). The proposed approach enhances the efficacy of therapy while decreasing side effects.

Scientists have been studying targeted ligands like aptamers, amino acids, and antigens to reach this goal. It combines nanoparticles that deliver chemotherapy

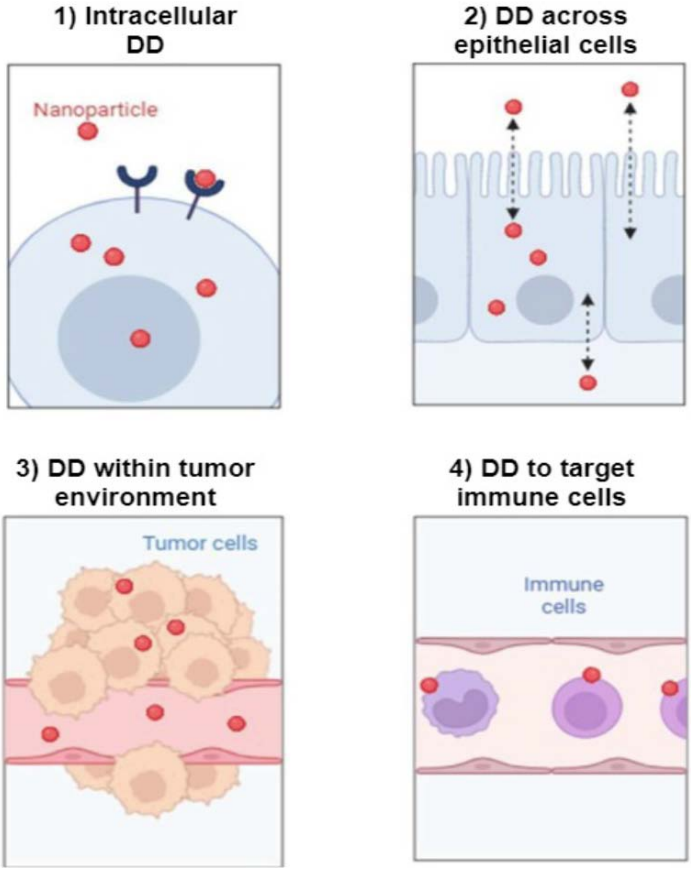

Figure 4: Targeted NP-based DDM [4].

with monoclonal antibodies that bind to TC receptors. This method improves patient outcomes while minimizing side effects, making the drug more effective against TC and limiting damage to healthy tissues. When tumors are heterogeneous, which means that different cells make different amounts of the target antigen, this method does not work. Targeted DDM may also not work well in tumors where microbiomes stop antibodies or nanoparticles from getting inside the tumor.

7. RECENT ADVANCES IN NP-BASED DDM

Medicine has greatly changed since NP-mediated DDM and its controlled medical use came along. Nanotechnology has recently made it possible to create new drug carriers that have better pharmacology, lower toxicity, and improved biological compatibility. Some of the long-term conditions that these new technologies are changing the way doctors treat are diabetes, cancer, heart disease, and neurological disorders.

It is a big step forward in nanoparticle-mediated DDM that NPs can respond to stimuli of any kind. When the pH, temperature, or enzyme activity changes or other biological or environmental factors happen, these nanoparticles let go of their cargo. This targeted approach improves both the effectiveness and safety of medications. Much research has been done on how pH-sensitive liposomes and polymeric nanoparticles could treat cancer because they can selectively release drug-like substances in the acidic environment around tumors.

Using lipid-based NPs, like solid lipid NPs (SLNs) and nanostructured lipid carriers (NLCs), is a new idea. Some benefits these carriers offer are better drug stability, longer-release, and higher bioavailability. Liposome nanoparticles work well at delivering genetic material in COVID-19 mRNA vaccines. Due to progress in multifunctional NPs, it is now possible to combine imaging agents with therapeutic chemicals into a single nanosystem that sticks together. These theranostic nanoparticles help with personalized treatment by letting drugs be delivered in real-time and monitoring how well they are working.

More research is being done on how gold NPs, quantum dots, and iron oxide NPs can be used for imaging and therapy. Even with these improvements, problems like getting approval from the government, possible long-term harm, and mass production still exist. Researchers work hard to solve these problems by changing the surfaces in new ways, breaking down materials, and using precise engineering.

New developments in NP-mediated DDM will change the future of medicine by making treatments more effective, keeping patients safer, and allowing for more personalized care. Due to ongoing research and clinical trials, these technologies will eventually change how people with diabetes mellitus type 2 (DM2) are treated and how the disease is managed worldwide. In the future, AI-assisted nanoparticles should be enabled through a precise optimization for the targeted delivery, which is personalized through nanomedicine treated to individual tumor profiles. Based on stimulation, the responsive system helps to enhance and release the drug in response to the tumor-specific triggers in enzymes.

8. CONCLUSION

The ability of NPs to act as an effective DDM has led to a lot of research and the use of nanotechnology in cancer treatment. Generally, NP-based DDMs have demonstrated considerable promise in combating DR. The PT has notably improved drug absorption at the TC site through the permeability and retention effect, while the AT has significantly enhanced it via peptides. Secondly, due to the intricacy of tumors, mixed therapy has emerged as the predominant approach to medical treatment. Nonetheless, various antitumor agents demonstrate distinct drug kinetics and DDM properties, resulting in the inability of present chemotherapy treatments to precisely administer multiple drug ingredients to a single TC simultaneously, thereby impacting the synergistic efficacy of the integrated therapy. The NP-based DDM have offered an effective method to integrate several drug elements within the same NP to attain a coordinated effect. Researchers are looking for ways to extend the life of nanoparticles by altering their chemical makeup and covering them with protective materials. To lower the risk of side effects even more, we carefully select physiologically appropriate materials for making NPs and do thorough toxicity assessments before clinical trials. In future research, the focus will be on integrating AI for predictive nanoparticle design, which also helps to enhance biomarker profiling and develop a clinically translatable responsive system. Personalized nanomedicine approaches are also used for overcoming these issues.

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