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Targeted and efficient therapeutic effect of nanoparticles against malignant tumor

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Abstract

Cancer or malignant tumors are major global health concerns and limited treatment regimens are hazardous threats to people. Mostly malignant tumors are caused by various genetic and environmental factors. Various chemical agents have been used over the years to treat and limit this disease but due to unsatisfactory and insufficient results, researchers have diverted their attention towards alternatives. Nanoparticles (NPs) have a major role in improving treatment facilities. Nanoparticles have peculiar characteristics due to their size, shape, charge, and surface area. Their unique properties allow improved drug delivery to the target site at the cellular level by active or passive targeting. Different NPs are being modified for cancer therapy like polymeric NPs, liposomes, extracellular vesicles, nano-emulsions, carbon NPs, quantum dots, magnetic NPs, and silica NPs. They hold a promising future for diagnosis, treatment, and lowering the risk of these lethal diseases including breast and brain cancer due to their various beneficial mechanisms of overcoming drug resistance mechanisms.

1. Introduction

Cancer has been known for a long time and has been the number one cause of death among people worldwide. Cancer has been recognized by many ancient civilizations, including the Egyptians. However, as it often develops later in life, its prevalence wasn't widely understood in the 19th century (Afify and Seno 2023). Cancer has the potential of occurring at any age but mostly it effects the adults, and the ratio has been considered to be as at least one in three will develop cancer and among them one in four men dies and one in five women dies (Haj-Mirzaian et al. 2021). Cancer is not confined to only humans or mammals, but also almost all multicellular animals, and needs to be controlled and prevented (Dujon et al. 2021). In a study in 2007, it was concluded that cancer nearly killed ~7,900,000 people worldwide, a value that represents ~13% of total deaths. So, there is a dire need to control this lethal disease in the living population (Shewach and Kuchta 2009).

Cancer can be defined basically as any uncontrollable abnormal growth that disregards the normal rule of cell growth (Yadav and Mohite 2020). Unlike normal cells, which receive signals to self-destruct, cancer cells ignore these signals and multiply uncontrollably (Chaudhry et al. 2022). If this remains uncontrolled it can result in a condition called as metastasis, and that becomes the basis of most of the deaths, almost 90 % (Webster et al. 2017). There is a prevailing theory suggesting that cancer cells develop as a result of the disruption in the networks at molecular, biological, and cellular levels that control the proliferation, differentiation, and cell death (Kashyap and Dubey 2022). After research of over 50 years, cancer is defined as a disease involving changes or mutations in the cell genome (Yildirim et al. 2023). These changes in the DNA result in the formation of proteins involved in the maintenance of a delicate balance between cell division and quiescence, which in turn results in cells that then continue to divide (Linher-

Melville and Singh. 2016). The cancerous growth is mainly divided into two types based on the spread of the tumor. They can be either benign tumors or malignant tumors (Sinha 2018). Benign tumors are mainly not able to invade the surrounding tissues spreading their negative effects on the surrounding tissues and they somewhat resemble the tissue of origin. They are separated by the surrounding tissue, by the connective tissue capsule (Boutry et al. 2022). On the other hand, malignant tumors are more dangerous as they have two main features, they are capable of involving the other tissues and also result in dyskariosis (cell abnormalities). In this case, there might be an increase in the cell size and shape, nucleus size may increase and its density of staining also increases (Grigore et al. 2017).

In the past centuries, Numerous methods, including chemotherapy, radiation therapy, and surgical removal, have been employed to combat cancer (Current 2020). These treatment methods have proven to be very effective in many cancerous growths in various regions of the body like epithelial cell tumors, colon cancer, and many others (Lentz 2001). As the tumor or cancer cells gain the capability to invade the other cells and metastasize the chances of the survival of the patient or the treatment of the cancer reduces (Rajput et al. 2023). Cancer chemotherapeutics have played a significant role in the treatment of different types of cancers over the years, but as the technologies are modernizing the use of nanomaterials is gaining more significance in the treatment of cancerous growths (Kumar et al. 2023). Nanoparticles (NPs) have emerged as powerful tools in medicine, offering unique properties like size, chemical reactivity, absorption capacity, and biological motility (Shelin and Meenakshi 2023). They are very valuable in various kinds of analysis and therapies that may otherwise not be possible. Nanoparticles have the potential to act as active carriers for the anticancer agents to the site of action and cause minimum damage to normal tissues (de Sousa et al. 2022). They are capable of altering and improving the physico-kinetic and physico-dynamic properties of various types of drugs. They are beneficial in many therapeutic actions and are gaining more significance in this field due to their efficient drug delivery systems (Rao et al. 2022).

Nanotechnology is gaining insights in the medical field and has proved to be effective in the treatment of various diseases (Xie 2023). One of the key advantages of nanoparticles (NPs) is their larger size compared to conventional drugs, allowing for manipulation to improve their therapeutic activity and safety (Anjum 2022). NPs also show unique electromagnetic properties that can be exploited for therapeutic purposes (Iovine et al. 2017). Another big advantage of the NPs is their ability to differentiate between the pathological and normal cells. This unique property of nanoparticles makes them very useful for many therapeutic purposes (Ramrakhiani 2022). These properties allows them to be used as effective medications against cancer cells (Alrushaid et al. 2023). The formulation of cancer nanomedicines is mainly based on liposomes (e.g., Doxil1, Onivyde1, and Vyxeos1; encapsulating either hydrophilic or hydrophobic molecules), polymeric micelles (e.g. Genexol-PM, NK105, and NC-6004; encapsulating hydrophobic therapies), albumin (e.g. Abraxane 1), or inorganic NPs (e.g. NanoTherm and NBTXR3) (do Nascimento et al. 2020). Doxil became the first liposome-formulated NP-based drug used for cancer treatment. Since then, many NP-based drugs have been introduced for cancer treatment (Fulton and Najahi-Missaoui 2023). These are the organic or inorganic particles applied topically, locally, and systemically. The NPs that are clinically approved are categorized on the basis of the material composition as the lipid, polymer, protein, or metal-based NP category (Raszewska-Famielec and Flieger 2022). There are some medications that are used for intra-tumoral administration. Here the NPs may accumulate in the tumor site and this may be categorized in the passive and active targeting strategies. Various NP anticancer drugs have been formulated (Melero et al. 2021).

2. Key principles of nano-medicine in cancer therapy

NPs can be used as they may overcome the solubility and stability issues of the anticancer drugs. By encapsulating these drugs within hydrophilic nano-carriers, their low solubility and stability can be

Table 1 Cancer nanomedicines (Norouzi et al. 2020; Wolfram and Ferrari 2019)

Product	Drug	Carrier components	NP size (nm)	Function	Cancer type
Doxil ®	DOX	Liposome	80-90	Immuno-evasion	HIV-related Kaposi sarcoma, ovarian cancer, and multiple myeloma
Myocet ®	DOX	Liposome	150	Inhibit growth of cancer cells	Metastatic breast cancer
Abraxane ® nab-PTX	Paclitaxel (PTX)	Human serum albumin NPs	130	Solubilization/Sustained Release	Breast, lung, and pancreatic cancer
Mepact ®	Mifamurtide	Liposome	-	Unique transport properties, Enhanced permeability and retention (EPR) effect	osteosarcoma
Marqibo®	Vincristine sulphate	Liposome	115	Solubilization/Sustained Release	Acute lymphoblastic leukemia
Onivyde ®	Irinotecan	Liposome	110	Immunoevasion	Advanced pancreatic cancer
Vyxeos ® (CPX-351)	Cytarabine and daunorubicin	Liposome	100	Combination therapy	High-risk acute myeloid leukemia
Apealea ®	Paclitaxel (PTX)	Micelle	20-30		Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer
Genexol-PM ®	Paclitaxel (PTX)	Micelle	23.9	Solubilization/ Sustained Release	Breast, lung, and ovarian cancer
Nanotherm	Aminosilane coated SPIONs	NP	15	Unique electromagnetic properties	Brain tumors

significantly enhanced (Hashim and Dirisala 2022). At the same time, the chemical stability of the anticancer drug can also be increased. P13K inhibitor and radiosensitizer wortmannin drugs were stopped due to their lower solubility and stability, but using a lipid-based nano-carrier system, the solubility of wortmannin was improved from 4 mg/L to 20 g/L and the stability in vivo also improved (Wolfram and Ferrari 2019). NPs can also provide protection to the anticancer drugs from bio-degradation or excretion thus influencing the pharmacokinetic profile of the compound. Encapsulating the anticancer agents by the nano-carrier prevents the degradation of the drug by the enzymes (Kumar and Anis 2023). NPs can also play an important role in the targeting and distribution of anti-tumor medications (Hamdy et al. 2022). Nanocarriers can facilitate cellular drug uptake through both active and passive mechanisms (Afzal et al. 2022). They also have the ability to target the cells selectively (Saini 2022). There are examples showing that some drugs whose delivery is not dependent on the pH, such as doxorubicin, can be conjugated with the pH-sensitive NP to improve the cellular drug uptake and the intracellular drug release (Li 2023). Furthermore, NPs can reduce tumor cell resistance to anticancer drugs, extend drug circulation time, mediate stimuli-responsive drug release, and enhance endocytic drug uptake (Gu et al. 2021). This overall leads to the reduced resistance of the tumor cells against the targeted nano-carriers (Hassanin et al. 2022).

Passive targeting

Most nano-based cancer therapies rely on passive targeting, which manipulates the physicochemical properties of the compound (Ji and Li 2022). The enhanced permeability and retention effect (EPR) promotes the nanomedicine drug accumulation in tumor. This effect is based on the presence of the leaky intra-tumoral blood vessels whose endothelium is fenestrated and has pores of various sizes ranging between 100 nm and 780 nm size (Kim et al. 2023). Nanomedicines can be directed to the tumor site without the need for ligand attachment to the nano-carrier surface (Zhong et al. 2023). There can be some cytotoxic effects which include heterogeneity of stroma, any hypoxic gradient can be involved in severely impacting the efficacy of drugs delivered passively (Sharma et al. 2019). Furthermore, the interstitial fluid pressure may limit the drug delivery. Some extracellular malignancies like the pancreatic cancer may also hinder the penetration of the drug (Fu et al. 2022). Finally, passive targeting is not beneficial in preventing any kind of accumulation of the nano-carriers in the organs with the fenestrated epithelium e.g. the liver and spleen (Attia et al. 2019). So there comes a need of development of second-generation nanomedicine compounds that may improve targeting and increase the specificity of the compound (Tracey et al. 2021).

Active targeting

In this case, a high-affinity ligand is attached to the nano-carrier surface to ensure highly specific delivery. The ligand selectively binds to the receptor site of the target organ or tissue (Dey et al. 2023). The wide range of the ligands used for these purposes include folic acids, carbohydrates, or macromolecules such as peptides, proteins, antibodies, aptamers, and oligonucleotides (Kapoor et al. 2019). The ligand must be carefully chosen to avoid adverse effects while maximizing binding to target cells and minimizing binding to normal cells (Yoo et al. 2019). The density of the target ligands needs to be optimized so as to maintain the stealth properties and avoid any rapid recognition by the reticuloendothelial system (RES). It ensures the optimal internalization of the compound and high targeting efficiency

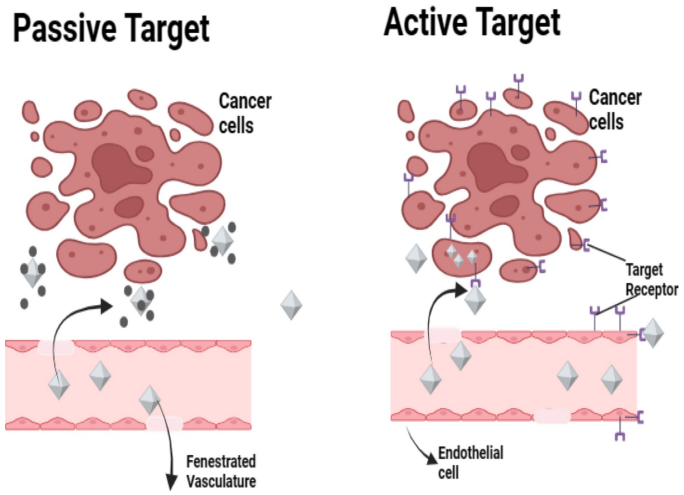

***Fig. 1**: Delivery of carriers to tumor tissue (a) Passive Target: NPs transported through leaky vessels and unique intra-organ tumor pressure (b) Active target: NPs designed to adhere to specific biological structures in tumors via the molecular recognition of surface-bound ligands (biorender.com)*

(Adeyemi et al. 2019). There can be some anatomic and physiological barriers that may be a hindrance between the target and nano-carriers. This limitation can be overcome by active targeting of the tumor vasculature (Lenders et al. 2023). Actively targeted nanoparticulate delivery can enhance the drug retention in tumor due to various reasons including the increased cellular binding, minimizing non-specific uptake, and circumventing the resistance mechanisms (Tian et al. 2022).

3. Structure of NPs for cancer treatment

Generally, structure is composed of the core, shell, and surface. The core consists of inactive matrix, the active agent itself or active agent containing matrix and determines the particle size (Kumar et al. 2020). The shell acts as the base to which the surface molecules may be anchored or bound with or without intermediate spacers (Goracinova et al. 2018). The surface molecule is actively involved in the bio-distribution of the NPs consisting of site, tissue, cell or receptor specific molecules (Yoo et al. 2019). The mode of bonding (physical adsorption or covalent bonding) used in the construction of the particle is very important and to achieve optimal biodistribution and active agent delivery in cancer treatment and diagnosis, the rate and timing of component release and degradation from the particles must be carefully controlled (Huang et al. 2023). The NPs have then to be degraded from the body and eliminated by globular filtration (Poon et al. 2019).

4. NPs in cancer therapy

NPs are extensively being used for the therapeutic purposes, drug delivery systems, and cancer therapy (Nicoletta and Iemma 2023).

Organic NPs

Polymeric NPs

They are well defined as "colloidal macromolecules" formed by different monomers having a special architecture. To achieve regulated drug release, the drug is either encapsulated within or attached to the NP exterior, forming a nanocapsule. This configuration enables controlled drug release at the target site (Escudero 2022). Previously

used toxicity causing, non-biodegradable polymers, like polyacrylamide, polystyrene are being replaced by the bio degradable polymers such as polylactic acid, chitosan, alginate, and albumin which are known to reduce toxicity and enhance drug release and biocompatibility (Kucuk et al. 2023). A study showed that indomethacin loaded nano-capsule can substantially decrease the size of the tumor (Franco et al. 2022). Examples of anticancer drugs under clinical development include paclitaxel poliglumex (Xyotax), HPMA copolymer-platinate (AP 5280), Modified dextran-camptothecin (Prothecan), etc. (Tiwari et al. 2023).

Dendrimers

They are spherical polymeric macromolecules having a defined hyperbranched architecture (Mishra 2023). Their synthesis is initiated by reaction between the ammonia core and acrylic acid. An intermediate is formed which then reacts with ethylenediamine to yield a "tri-amine", which subsequently reacts with acrylic acid to produce a "hexa-acid". This iterative process continues, generating "hexa-amine" Generation 1 and subsequent generation (Gavas et al. 2021). Size ranges from 1-10 nm reaching up to 15 nm. The synthesized dendrimers significantly delay the growth of the epithelial cancer xenografts (Tran et al. 2013).

Monoclonal antibodies (mAB) NPs

Monoclonal antibodies have particular targeting abilities due to which they are widely used in cancer treatment (Srirapu 2023). By combining mAbs with nanoparticles (NPs), researchers have developed antibody-drug conjugates (ADCs) that offer enhanced specificity and efficacy compared to cytotoxic drugs or mAbs alone (Lewis 2023). For example, an antibody–drug NP consisting of paclitaxel core and a surface modified with trastuzumab proved to have a better anti-tumor efficacy and lower toxicity than single-agent paclitaxel or trastuzumab alone in cancer treatment (Sakhi et al. 2022).

Liposomes

These can be uni-lamellar or multi-lamellar to encapsulate the drug molecules. They are basically spherical vesicles comprising phospholipids (Nakhaei et al. 2021). Liposomes based nanoscale drugs were the first ones to be approved. Typical liposomes have a unique architecture composed of "hydrophobic phospholipid bilayer" and a "hydrophilic core" which allows it to entrap both hydrophobic and hydrophilic drugs which protects the environmental degradation of the drug in circulation (Khafoor et al. 2023). Examples of drugs encapsulated in liposomes include doxorubicin, paclitaxel, and nucleic acids, which demonstrate high anti-tumor efficacy and enhanced bioavailability (Fulton and Najahi-Missaoui 2023).

Extracellular vesicles

These are double layered phospholipid vesicles ranging from 50-1000 nm in size (Lange 2023). These are continuously secreted and are of three main classes: exosomes, microvesicles, and apoptotic bodies (Gregory and Rimmer 2023). Exosome-based nanoparticles (NPs) are particularly effective at evading immune surveillance and rapidly internalizing into cancer cells, serving as natural vehicles for delivering cytotoxic and other anti-tumor drugs to target sites. Exosomes loaded with doxorubicin (exoDOX) are a prime example of this approach, demonstrating efficacy in treating breast cancer (Gomes et al. 2022; Hosseinikhah et al. 2023).

Nanoemulsions

These are colloidal NPs with heterogeneous mixtures of oil droplets in aqueous media ranging from 10-500 nm (Goswami et al. 2023). They are of three types - (i) oil-in-water system, (ii) water-in-oil system, and (iii) bi-continuous nano-emulsion (Dhumal et al. 2022). Nanoemulsions, loaded with the spirulina and paclitaxel, show improved anti-tumor effect by regulating immunity through some pathways (Gavas et al. 2021).

Inorganic nanoparticles

Carbon NPs

Carbon-based nanomaterials, including graphene oxide (GO), fullerenes, and carbon nanotubes (CNTs), are widely used in medical applications due to their biocompatibility and unique optical, mechanical, and electronic properties. These materials can encapsulate drugs through π-π stacking (Owida et al. 2023). There are various categorizations of the carbon NPs which are further divided on the basis of their properties and composition (Bellucci 2020). Graphine oxide (GO)-doxorubicin exhibit high anticancer activities mainly in breast cancer (Itoo et al. 2023). PEG-modified fullerenes (large carbon cage molecules composed of carbon allotrope with different conformation types) show promising photodynamic effects on the tumor cells (Ku et al. 2016). Carbon nanotubes (CNTs) are efficient in bringing an immune response and thus suppressing the tumor growth (Zhang et al. 2006). Fluorescent single-walled CNT with mAB that encapsulate doxorubicin can be used to target the colon cancer cells (Gavas et al. 2021).

Quantum Dots

These are nanometer scale semiconductors having a broad spectrum of absorption, narrow emission bands and high photostability which allow them to be extensively used in the biological imaging (Panja and Patra 2023). Besides this biological imaging, the quantum dots are also being used against the cancer. The quantum dots aptamer-doxorubicin conjugate is able to target the prostate cancer cells (Davodabadi et al. 2023).

Metallic NPs

They are majorly used in the biological imaging due to their optical, magnetic, and photothermal properties. Gold NPs, silver NPs, iron-based NPs, and copper NPs are commonly used metallic NPs (Shetty et al. 2023). For instance, anti-HER2 functionalized gold-on-silica nanoshells have shown promise in targeting HER2-positive breast cancer cells. Additionally, an iron oxide NP formulation known as Combidex® is currently in late-stage clinical trials for detecting nodal metastases. Furthermore, Feraheme®, a ferumoxytol-containing iron oxide NP formulation, is being used to treat nodal metastases in prostate and testicular cancer (Gavas et al. 2021).

Magnetic NPs

These NPs are widely used in MRI imaging and drug delivery contains metal or metal oxides (Subhan 2022). Breast cancer can be effectively targeted and imaging can also be done by the Luteinizing Hormone-Releasing Hormone-conjugated superparamagentic iron oxide NPs (Gavas et al. 2021). Some magnetic NPs can also be used in magnetic hyperthermia for thermal ablation of cancer cells (Pullar 2023). Ferifex ® and Resovist ® are under clinical trials to be used against the liver metastasis and colon cancer (Gavas et al. 2021).

Silica NPs

These NPs are significantly used to deliver genes by functionalizing the NP surface with amino-silicanes (Petreanu et al. 2023). They have been extensively used for immunotherapy. Colorectal cancer cells have shown successful uptake of camptothecin-loaded mesoporous silica NPs (Theivendran et al. 2023).

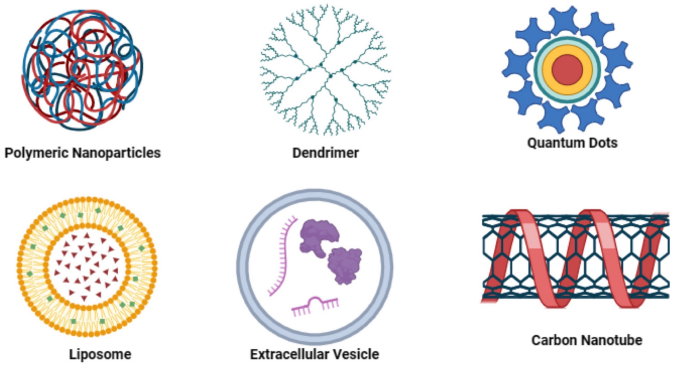

***Fig. 2**: Different NPs used in cancer drug delivery system (biorender.com)*

5. Mechanism of action of the NPs against cancer

NPs are widely being used against cancer due to various benefits they offers like low toxic effects, enhanced selectivity, improved penetration, and biocompatibility. By altering the drug toxicity profile, NPs can target cancer cells more effectively. Their ability to easily penetrate cancer cells and specifically deliver drugs to the tumor site minimizes off-target toxicity By using tumor-specific constituents, nanomaterials can target the cancer cells by greater affinity (Sarvari and Sarvari 2023). Moreover, it can bypass the bottlenecks of indiscriminate bio-distribution and high dosage for administration. They can also form reactive oxygen species within the cancer cells that can elicit a cytotoxic response on the cancer cells causing regression of the tumor cell. Hence, its environment-friendly nature, little or no adverse effects, and specific action on the target site make it a promising alternative to other methods of tumor control (Poon et al. 2019). Fig. 3 Illustrates the mechanism of action of the NPs against cancer cells.

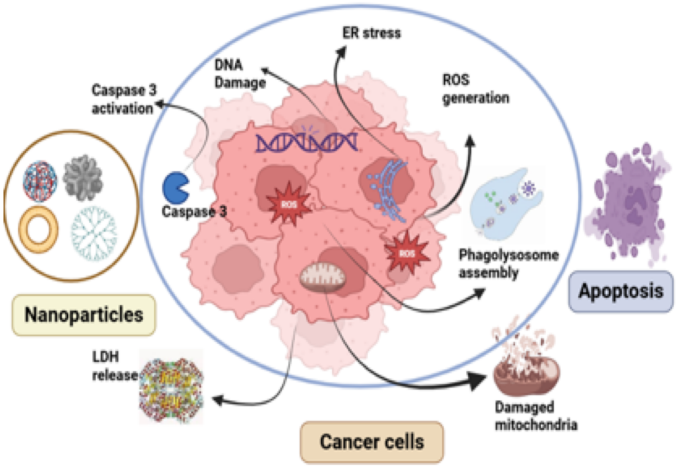

***Fig. 3**: Mechanism of actin of NPs against cancel cells (biorender.com)*

6. Utilization of the NPs for cancer treatment

NPs have been recognized as important players in the treatment of cancers recently. Various NPs like lipid-based, polymer-based, inorganic, viral, and drug-conjugated NPs are investigated for their roles in cancer therapy (Hegde et al. 2023). NPs are very effective in treating cancer in vitro as well as in vivo due to their advantages like the targeted delivery to the tumor, tumor imaging, the ability to store several drug molecules, and their properties of overcoming solubility, stability, and resistant problems (Mohanty et al. 2020). Several NP-based therapies have received FDA approval, including Daunoxome, Doxil, Depocyt, Abraxane, and Oncaspar, which are effective in treating various cancers such as ovarian, breast, lung, and renal cancer (Aghebati-Maleki et al. 2020).

7. NPs in the diagnosis and treatment of breast cancer

Despite significant advancements in treatment strategies, breast cancer remains a prevalent health concern. While traditional therapies such as surgery, radiation therapy, and hormone therapy offer benefits, they also come with limitations and side effects (Mumtaz et al. 2023). It was known that the chemotherapeutic agent, tamoxifen, resulted in cancer in the endometrial tissue so there was a need for a new system having less or nearly no side effects (Emons et al. 2020). NPs are widely being used for protection of healthy tissues and the eradication of cancer cells. Liposomal anthracycline can be used for all levels of breast cancer but use is limited due to toxic effects on the heart (Lao et al. 2013). A more efficacious outcome can be achieved by hybridization of the liposomal anthracycline with a monoclonal antibody against human epidermal growth factor receptor 2 or HER2/neu (Aghebati-Maleki et al. 2020). If liposome is combined with doxorubicin-contained liposomes then it has higher efficiency in treating metastatic cancer. Central NPs containing paclitaxel surrounded by albumin are also highly efficient in carrying hydrophobic molecules in breast cancer (Gomes et al. 2022). Using NPs in combination with tamoxifen by targeted delivery can increase their penetrability in tumor tissue. The quantum dots can be highly used in identification of the cancer cells (Amraee et al. 2023). They can conjugate with the different antibodies for specific proteins and the immunofluorescence produced by them can help in the recognition of the targeted cancerous cells increasing their sensitivity (Van Zundert et al. 2021). The best method is the conjugation of quantum dots with antibodies and peptides of streptavidin and biotin as adaptor molecules (Tran and Park 2021).

8. Application of NPs in the diagnosis and treatment of brain cancer

The blood-brain barrier (BBB) presents a significant challenge in the treatment of brain-related diseases, limiting the effectiveness of many therapies. By carefully designing and administering nanoparticles (NPs), it is possible to overcome these limitations and improve the treatment of brain cancer (Vanbilloen et al. 2023). Fe_3O4, monocrystalline Fe_3O4 NP, were the first NPs to be used in brain tumor imaging as they were connected to the tumor-specific L6 monoclonal antibodies. Organic NPs including the liposomes and the dendrimers are mainly used as the diagnostic NPs for brain cancer treatment. Inorganic NPs like Fe_3O4 and gold have been studied for brain cancer treatment. Organic NPs, polymers, liposomes, dendrimers, and hydrogels have also been studied for brain cancer treatment (Caraway et al. 2022). Quantum dots (QDs), Fe_3O4 NPs, Au NPs, and polymers

indicated higher treatment success in comparison with theranostic NPs. All of them are being used as carriers for drug delivery and imaging (Aghebati-Maleki et al. 2020).

9. Mechanisms of NPs in overcoming drug resistance

This phenomenon of becoming tolerant to the pharmaceutical treatments prevails across all types of cancers and is one of the chief problems in cancer therapy (Dhanyamraju et al. 2022). It can be of two types (i) Innate: Pre-existing mutations in genes involved in cell growth and apoptosis (ii) Acquired: Resistance developed after the anti-tumor medication (Gavas et al. 2021). NPs can be used here to overcome the resistance due to their extraordinary ability to co-encapsulate multiple therapeutic agents (Hu et al. 2022).

Targeting Efflux mechanisms

This is one of the major mechanisms of the tumor cells that result in the pumping out of the drugs due to the over-expression of the P-glycoproteins. They have been linked with the drug resistance or inadequate treatment response, particularly in breast and ovarian cancers (Hano et al. 2018). NPs can be used for overcoming these efflux mechanisms. By entering cells through endocytosis rather than diffusion, NPs can bypass efflux pumps and deliver drugs directly to the perinuclear region (Lenders et al. 2023). Additionally, by utilizing pH-sensitive or redox-responsive release mechanisms (Gupta et al. 2017), NPs can further evade efflux pumps and ensure controlled drug release. Another strategy involves co-delivering chemotherapeutic agents with efflux pump inhibitors using NPs (Zhang et al. 2017). For instance, a recent study demonstrated the effectiveness of NPs co-delivering COX-2 inhibitors and doxorubicin in overcoming drug resistance in breast cancer. Similarly, silica NPs encapsulating miRNA-495 and doxorubicin have shown promise in overcoming resistance in lung cancer cells (Gavas et al. 2021).

Targeting an apoptotic pathway

The main mechanism of abnormal cell proliferation is due to the activation of the faulty apoptotic pathway by the deregulation of Bcl-2 and nuclear factor kappa B (NF κB). These anti-apoptotic proteins can be potentially targeted to reverse the drug resistance (Gavas et al. 2021). NF κB inhibitors have been used in combination with the "pyrrolidine dithiocarbamate" (PDTC) and "curcumin" (Shin et al. 2023). Instead of suppressing the anti-apoptotic proteins, pro-apoptotic pathways can be triggered to fight the apoptotic pathway-mediated drug resistance. A combination of ceramide and paclitaxel is a good example (Dogan et al. 2022). Similarly, transfecting the p53 gene by poly(lactic-co-glyclic acid) has been carried out in models of breast cancer that show potent induction of apoptosis and tumor growth inhibition (Piao et al. 2023). Co-delivery of doxorubicin and resveratrol encapsulated in NPs has shown cellular toxicity on doxorubicin resistant breast cancer cells mainly by the down-regulation of the expression of Bcl-2 and NF-κB, thereby initiating apoptosis and also efflux transporter expression inhibition (Gavas et al. 2021). Folic acid-conjugated planetary ball milled NPs encapsulated with resveratrol and docetaxel were used on multi-drug resistant prostate cancer cells, and they proved effective due to their mechanism of downregulating anti-apoptotic genes (Jurczyk et al. 2022).

Targeting Hypoxia

Some tumor cells are rapidly in a hypoxic condition due to the abnormal blood vessels in vicinity of the tumor cells (Steinberger 2023). The part of tumor cells in a hypoxic condition often escapes the chemotherapy drugs as hypoxia creates an oxygen ramp inside the tumor intensifying the heterogenicity of the tumor and encouraging a more aggressive phenotype (Gavas et al. 2021). Moreover, hypoxia may allow the overexpression of the efflux mechanisms (Ebbensgaard et al. 2020). The major protein playing an important role is the hypoxia-inducible factor 1 α (HIF-1α), which needs to be silenced or targeted to overcome resistance (Terzic et al. 2023). This hypoxia-induced drug resistance can be reduced by using NPs containing HIF-1 α siRNA. Indirect inhibition of HIF-1 α can be done too. "PI3K/Akt/mTOR pathway" can control the expression of HIF-1. If this pathway is inhibited the expression of HIF-1 α can be effectively inhibited which enhances the sensitivity of resistant cells to cancer treatment (Gavas et al. 2021). NPs like PLGA-PEg and PEGylated and non-PEGylated liposomes can be effectively used (Peng et al. 2023). Additionally, inhibiting heat shock protein 90 (HSP90), which is involved in HIF-1α stabilization, can enhance the efficacy of cancer therapy. For example, 17-AAG-loaded NPs have shown promise in overcoming resistance in bladder cancer treatment. By targeting key pathways involved in hypoxia-induced drug resistance and utilizing advanced nanotechnology, researchers are developing innovative strategies to improve cancer therapy (Gavas et al. 2021).

10. Advantages of NPs in cancer therapy

The NPs have led to a whole new era of diagnosis, treatment, and management of cancer. They can either be used by active or passive targeting and effectively carry out their function and also overcome any resistance with minimum adverse reactions to the body (Gupta et al. 2024). Their temperature and pH sensitivity properties render them very effective in reaching their target sites. Moreover, there physicochemical properties like size, shape and surface chemistry have played a significant role on targeted drug delivery (Ullah et al. 2022). Cautious dosing is needed to effectively kill the cancer cells without causing any cytotoxic effects (Smita et al. 2022). Due to the surface modifications of the NPs the bypass mechanisms can be overcome and drug half-life is increased this way. NPs are known to cross the blood brain barrier and can also be used to prevent the degradation of the drug allowing more circulating time. This also enhances the stability of the drug (Zhao et al. 2023). NPs can be administered via different routes and can be very effective in carrying out their reaction. They can target the tumor cells by various mechanisms and have the ability to overcome the resistance of the tumor cells by various other mechanisms also (Roche et al. 2019).

11. Conclusion

Nanoparticles play an essential role against cancerous cells due to its various unique properties. It includes targeted delivery and evading the resistant mechanisms of the drug. They can further be modified to be used for specific tumors like brain and breast cancers. Clinical trials are also essential to assess the efficiency and impact of the NPs use. They can prove to be a beneficial therapeutic agent against the cancer in the near future due to their versatile properties and effective use. It can be a potential revolution in the cancer treatment and can lower the threats of this lethal disease.

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