Chapter 21

Nanobiotechnology for Breast Cancer Treatment

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Abstract

Despite many technological breakthroughs, even the best breast cancer treatments available today are not 100% effective. Chemotherapy has improved, but many drugs still do not reach the tumor site at effective doses and are often associated with high systemic toxicity and poor pharmacokinetics. Moreover, for many malignancies, diagnosis is obtainable only in metastatic stages of development, reducing the overall effectiveness of treatment. The choice of available treatments depends on tumor characteristics such as biomarkers, tumor size, metastatic disease, ligands, and antigen or endocrine receptor expression. Combined with surgical resection, chemotherapy and radiation remain the first line of treatment for patients with cancer. Even with these treatments, however, cancer continues to have high fatality rates and current therapeutic modalities have yet to significantly improve the often dismal prognosis of this disease. Nanotechnology is a highly focused approach, which may provide more effective and less toxic treatment when compared to chemotherapy. This area of research has emerged as cancer treatment in the form of new drugs and has reached promising results in preclinical and clinical trials proving its value as a potential tumor therapy.

Keywords: breast cancer, therapy, nanomaterials, nano-oncology

1. Introduction

Nanobiotechnology is defined as the biomedical application of nano-sized systems [1]. Nanomaterials, which measure a few nanometers in length, allow for unique interaction with biological systems at the molecular level. They can also facilitate important advances in detection, diagnosis, and treatment of human cancers and this approach is known as nano-oncology. Breast cancer is one of the most common cancers worldwide [2]. The choice of available treatments depends on tumor characteristics such as biomarkers, tumor size, metastatic disease, ligands, and antigens or endocrine receptors expression. Combined with surgical resection, chemotherapy and radiation remain the first line of treatment for patients

with cancer [3]. Improvements have been made to chemotherapies, because drugs are still not reaching the tumor site at effective doses, and are often associated with high systemic toxicities and poor pharmacokinetics. The nanotechnology is an approach which allows more effective and less toxic chemotherapy.

For many malignancies, diagnosis is obtainable only during metastatic stages of development, reducing the overall effectiveness of treatment [4]. Multidrug resistance, the principal mechanism by which many cancers develop resistance to drugs, is also a key factor in the failure of many forms of chemotherapy. It affects patients with a variety of blood cancers and solid tumors, including breast cancers [5]. Triple-negative breast cancer (TNBC), with absent or minimal expression of estrogen and progesterone receptors, and human epidermal growth factor receptor 2 are most common in younger women. In later stages, the prognosis is more dire, when compared to that of other breast cancer subtypes, with a higher risk of relapse, often involving other organs [6]. Emerging nanotechnologies have exhibited the possibility of specifically treating or targeting breast cancer. Among nanoparticles, various lipid nanoparticles, namely liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and lipid polymer hybrid nanoparticles, have been developed over the past few years for breast cancer therapy and evidence of this is documented [2].

Nanoparticles are also being actively developed for tumor imaging *in vivo*, biomolecular profiling of cancer biomarkers, and targeted drug delivery. These nanotechnology-based techniques can be widely applied for management of varying malignant diseases [7].

2. Breast cancer

2.1. Incidence and epidemiology

Breast cancer is the most frequent carcinoma in females and the second most common cause of cancer-related mortality in women worldwide. Approximately 61,000 new cases of *in situ* and 246,000 cases of invasive breast carcinoma, respectively, are expected to be diagnosed in the United States in 2016. Within this same period in the United States, breast cancer will account for an estimated 40,500 deaths among women [8]. The decline in cancer-related death rates over the past two decades has been driven by continued decreases in fatalities from breast cancer. Death rates for female breast cancer are down 36% from peak rates, most likely, as a result of improvements in early detection and treatment [9, 10]. By contrast, incidence rates increased in men for cancer of the breast. Some suggestive correlations about the increased cancer rate involve changes in environmental risk factors, such as obesity [8, 11].

2.2. Current breast cancer diagnosis and treatment

Breast cancer diagnosis, according to the European guidelines, is based on clinical examination in combination with imaging and confirmed by pathological assessment [3]. Clinical examination includes manual palpation of the breasts and locoregional lymph nodes, along with assessment for distant metastases (bones, liver, lungs, and neurological

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examination in the case of symptoms). Other forms of assessment include complete personal and family medical history, including evaluation of menopausal status, physical examination, blood count analysis, liver and renal function tests, and alkaline phosphatase and calcium checks [12].

Pathological diagnosis should be based on core-needle biopsies obtained by manual or preferably by ultrasound or stereotactic guidance. The pathological report should include the histological type, grade, estrogen receptor (ER), and for invasive cancer, progesterone receptor (PgR) along with human growth factor receptor type 2 (HER2) [13]. Routine staging evaluations are directed at locoregional diseases, as asymptomatic distant metastases are very rare and patients do not profit from comprehensive laboratory and radiological staging. Bilateral mammography and ultrasound of the breast and regional lymph nodes are included in imaging [3].

Subsequent to diagnosis, the prognostic and treatment are based on histology and immunohistochemistry (IHC) data. The selection of a treatment strategy is based upon the tumor extent/location (size and location of primary tumor, number of lesions, and number and extent of lymph node involvement) and other factors such as age, lifestyle, and general health status of the patient [14].

Women with a high risk of breast cancer (previous chest wall irradiation for lymphoma or carrying the BRCA1 or BRCA2 gene mutations) may be offered risk-reducing surgery including prophylactic bilateral mastectomy and reconstruction [15].

Ductal carcinoma *in situ* may be treated with breast conservation therapy (BCT), which has replaced radical mastectomy as the treatment of choice for early breast cancer, providing clear resection margins achieve, or with mastectomy, usually followed by radiotherapy and/or chemotherapy [16]. Whole-breast radiotherapy (WBRT) after breast-conserving surgery (BCS) for diagnosis of ductal carcinoma *in situ* (DCIS) decreases the risk of local recurrence [17]. Mastectomy may still be carried out based upon tumor size (relative to breast size), tumor multicentricity, prior radiation of the chest wall or breast, or patient choice [18]. Sentinel lymph node biopsy (SLNB) is now the standard of care. All modalities of chemotherapy, endocrine therapies (ETs), and targeted therapies as adjuvant treatments may be used preoperatively for patients with isolated tumor cells [13].

In HER2-positive breast cancer, trastuzumab therapy should be started in the neoadjuvant setting in association with the taxane part of the chemotherapy regimen. The chemotherapy regimens to be used in the neoadjuvant setting are the same ones used in the adjuvant setting. Unfortunately, there are no validated predictive markers which allow for the tailoring of the regimen to the individual patient. It is therefore recommended that a sequential program of anthracyclines and taxanes is used. ER-positive, HER2-negative carcinomas, especially of the lobular subtype, are generally less responsive to primary chemotherapy than ER-negative and HER2-positive tumors and may benefit more from primary ET. ET is usually given 4–6 months before surgery and continued postoperatively; for post-menopausal patients, aromatase inhibitors (AIs) are more effective than tamoxifen in decreasing tumor size and require less extensive surgery [3, 19].

2.3. Limitations of the current breast cancer treatments

One major challenge to the treatment of cancer is the lack of selective toxicity, which results in a reduced therapeutic index and, as consequence, compromises clinical prognosis. In order to reduce damage to normal tissues, suboptimal doses of anticancer chemotherapeutics are often administered [20].

Furthermore, the high interstitial fluid pressure (IFP) of solid tumors forms a barrier to transcapillary transport and results in poor biodistribution and penetration of drugs [21]. Another determinant of drug distribution within tissues is the half-life of the drugs in circulation; a drug with longer half-life will establish a more uniform distribution in tissues, even if its extravasation and penetration of tissues are relatively slow, whereas a drug that has a short half-life will have nonuniform distribution [22]. Moreover, vessels in tumor sites are heterogenic and may have fenestrations that increase the extravasation of drugs [23].

It has been shown that the amount of drug accumulated in normal viscera is 10- to 20-fold higher than that in a similarly weighted tumor site [24] and that many anticancer drugs are not able to penetrate more than 40–50 mm (equivalent to the combined diameter of three to five cells) from the vasculature [20, 25, 26]. These defects often lead to incomplete tumor response, multiple drug resistance (MDR), and ultimately therapeutic failure [27–29]. MDR, when tumor cells are treated with one anticancer drug and become resistant to a whole spectrum of drugs, is usually based on overexpressed drug efflux proteins and therefore is an important challenge for breast cancer therapy [30–33].

3. Nanobiotechnology-based platforms for breast cancer therapy

3.1. Properties of nanocarriers

The most current anticancer agents do not have an adequate job of differentiating between cancerous and normal cells and can lead to systemic toxicity and severe side effects. To overcome limitations of conventional chemotherapeutics, nanotechnology offers a more targeted approach and could therefore provide significant benefits to cancer patients. The size, shape, and charge are important parameters in nanoparticle systems that indicate the *in vivo* distribution, targeting ability, and biological destination of nanoparticles.

Nanoparticles have many advantages over free drugs. Some of them are listed below:

- Protect the drugs from early degradation.
- Enhance absorption of the drugs into a selected tissue.
- Control the drug tissue distribution and pharmacokinetic.
- Improve intracellular penetration.
- Prevent drugs from premature interaction with the biological environment.
- Reduce systemic toxicity.

Particles with hydrodynamic diameters below 10 nm are subject to rapid kidney clearance. Most of injected nanoparticles end up in the liver and spleen. Resident macrophages will phagocytose nanoparticles, degrade a small part of them, and exocytose both the degraded and intact nanoparticles. To avoid mechanical filtration by the liver and spleen, particles require size limitations above 200 nm [34, 35].

The zeta potential (surface charge) of nanoparticles has been shown to influence the nanoparticles direction within the tumor. It has been described that positively charged nanoparticles show increased cell uptake and binding due to the interaction between cationic nanoparticles and negatively charged cell membranes. Neutral particles have demonstrated lower interaction with the cell membrane than those nanoparticles with the same size and charge, resulting from the lower number of electrostatic interactions between charged cell membranes and nanoparticles surface [36–38]. In addition, studies have shown that systemically administered nanoparticles, with 30–40 nm [39] and 70 nm [40] in size and having a slightly negative surface charge, revealed internalization by tumor cells in mice and movement away from blood vessels [38].

Neutral polymers are used to minimize nanoparticle surface charge. The polymers are generally used to reduce aggregation caused by particle-particle interactions as well as limiting potential electrostatically induced interactions with other components of circulation, such as plasma membranes of cells (negative charge). Supposing the nanoparticle surface charge is increased, both positively and negatively, the probability that the particle will be removed from circulation by macrophage increases [36, 41]. When nanomaterials are administered into the blood, they are taken up within minutes or by the phagocytic cells of mononuclear phagocyte (MPS). The opsonization can be prevented by adding poly (ethylene) glycol (PEG) to the surface of nanomaterials. This addition drastically increases the blood half-life of all nanomaterials regardless of surface charge, improving the circulation time and accumulation in the target tissue. To create long-circulating nanoparticles, a diameter between 30 and 200 nm is desired [42].

The nanoparticle surface is the site that is modified to include targeting ligands. The reason for including a target ligand is that the cell surface of the cognate receptor is elevated in target cancer cells relative to other cells [43]. The advantages of surface coating are that it offers biocompatibilities, biodistribution of the nanoparticles, and modulating interaction between nanoparticles and cells, tissues, and biomolecules [44].

3.2. Nanoparticle drug delivery arsenal

To construct an appropriate nanocarrier for rapid and effective clinical translation, some important characteristics need to be considered. The nanocarriers must be made from a material that is biocompatible and easily functionalized along with being well characterized, soluble, exhibit extended circulation ability, no aggregation, and high uptake efficiency by the target cells.

Nanocarriers can be classified into three categories based upon materials that they are made from: (1) lipid-based, (2) polymeric, and (3) inorganic (**Figure 1**). These nanocarriers have been used for a variety of applications such as drug delivery, imaging, apoptosis detection, radiation sensitizers, and photothermic ablation of tumors [7, 45, 46]. Some of these nanocarriers are described below.

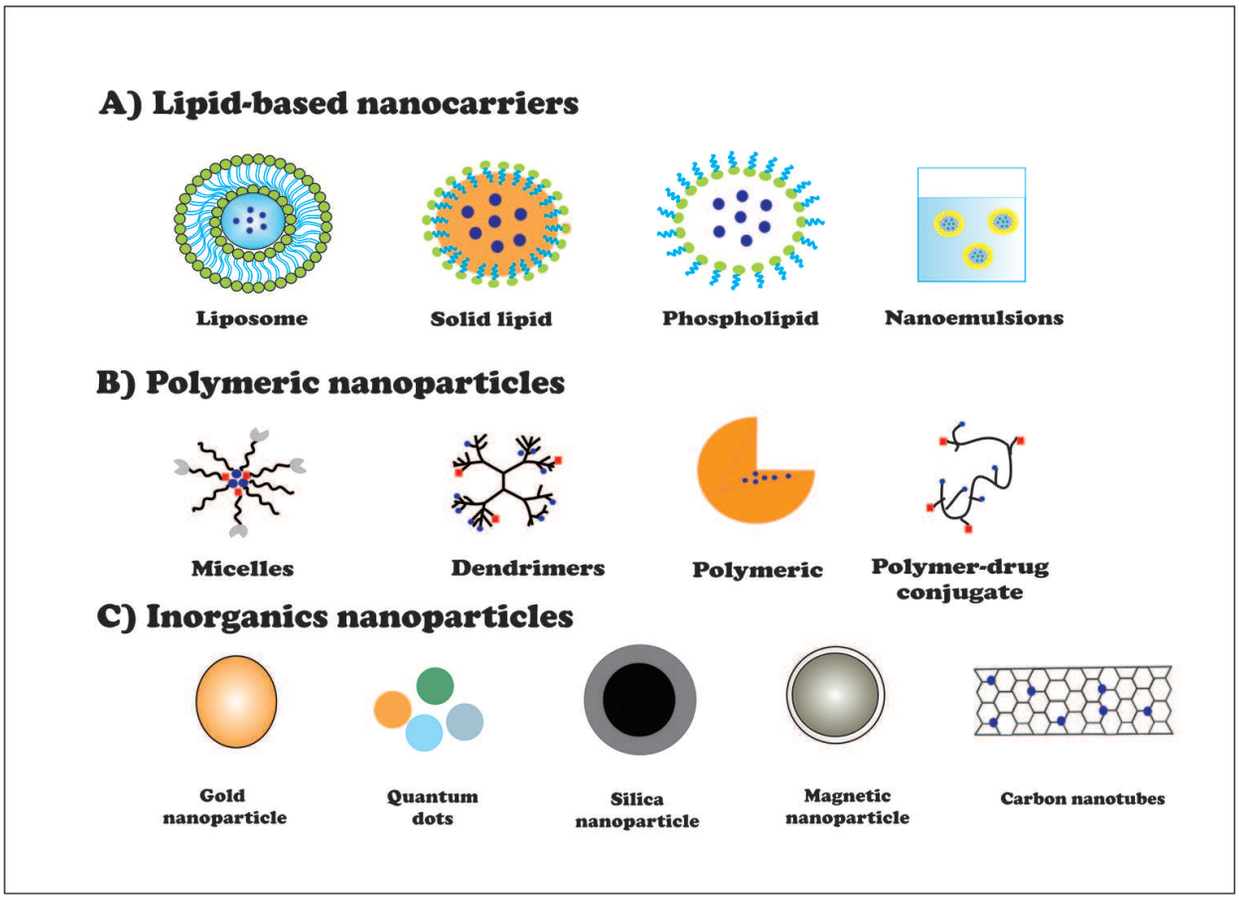

Figure 1. Schematic of different kinds of nanocarriers used for drug delivery. (A) Lipid-based nanocarriers, (B) polymeric nanoparticles, (C) inorganics particles.

3.2.1. Lipid-based nanocarriers

Lipid-based drug delivery systems have attractive properties, as well as biocompatibility, biodegradability, and the ability to entrap both hydrophobic and hydrophilic drugs. Lipid-based nanocarriers include liposomes, nanoemulsion, solid lipid nanoparticles, and phospholipid micelles.

Liposomes were the first nanocarriers, described in 1965 by Bangham [47], and the first that have been clinically approved by the FDA (Food and Drug Administration) to carry chemotherapy drugs (DaunoXome™) (50–80 nm) in 1996 [48]. Liposomes are small vesicles consisting of a bilayer lipid membrane surrounding an aqueous interior compartment [49]. The membranes consist of amphiphilic compounds, such as phospholipids and glycolipids, which make them biodegradable. Hydrophobic molecules are intercalated within the bilayer membrane, and hydrophilic molecules can be entrapped in their aqueous core, making liposomes a good therapeutic carrier [50]. To improve stability and circulation half-life, liposomes can be coated with targeting ligands and polymers such as PEG [51]. For example, a recent study showed that PEG-modified liposomes of ursolic acid enhanced *in vitro* cytotoxicity in gastric cancer cells when compared to standard ursolic acid [38]. Liposomal drug formulation improves the biodistribution and pharmacokinetics of a drug. This means higher drug

concentration can be achieved within tumors while reducing drug concentration in normal tissue [51]. Some disadvantages have been identified in the use of liposomes. Studies have shown that 50–80% of liposomes are adsorbed by the reticuloendothelial system (RES) and mainly by liver cells (Kupffer cells) within the first 15–30 min following intravenous administration [52, 53]. Other problems are related to their stability, poor batch-to-batch reproducibility, and difficulty with sterilization [54].

3.2.2. Polymeric

Polymeric nanoparticles systems are engineered from biocompatible and biodegradable polymers. Polymeric nanocarriers include micelles, dendrimers, and polymer-drug conjugates.

Many biodegradable polymers have been used to produce polymeric nanoparticles such as poly D L-lactic-co-glycolic acid (PLGA), poly D L-lactic acid (PLA), and poly ethylene glycol (PEG) [55]. Polysaccharides such as chitosan, alginate, and pectin have also been used to encapsulate these nanostructures [56, 57]. These nanoparticles are formulated through a self-assembly process using block copolymers with different hydrophilicity and consisting of two or more polymer chains [58]. Polymeric nanoparticles have been formulated to encapsulate either hydrophilic or hydrophobic drugs. This system facilitates surface modifications, and controlled pH- dependent controlled release [59]. A recent study revealed developed albumin-polymer conjugate nanoparticles of curcumin and demonstrated growth inhibition of three-dimensional LNCaP (epithelial cell line derived from a human prostate carcinoma) multicellular tumor spheroids when compared to native curcumin [60]. This result is an interesting option for controlled and target-based delivery.

Dendrimers are polymeric macromolecules with numerous arms extending from a center, resulting in a well-defined topological structure [61]. They have three main components: (1) a central core with two or more groups and repeated units attached to a central core called generations; (2) peripheral functional groups on the surface which determine the physicochemical properties of a dendrimer; (3) peripheral groups that can be modified to obtain both a charged hydrophilic and lipophilic function [62]. Dendrimers are appealing since they can be synthesized at various sizes, molecular weights, and chemical compositions [62]. With the modification of surface groups, interiors, and core, the properties of dendrimers can be optimized to obtain favorable physical characteristics, biodistribution, and receptor-mediated targeting. Dendrimers have shown promise for biomedical applications because they can be easily conjugated with targeting molecules, are biodegradable, biocompatible, and have high water solubility [63, 64]. A successful study using dendrimers was demonstrated in 2005 when methotrexate conjugated to polyamidoamine (PAMAM) dendrimers resulted in a 10-fold reduction in tumor size compared with that achieved using free systemic methotrexate [60]. In spite of promising results, dendrimers are relatively expensive as compared to other nanoparticles and require many repetitive steps in order to be synthesized, presenting a challenge for large-scale production [65].

3.2.3. Inorganic

The iron oxide nanoparticles (IO) are classified based on their sizes as standard superparamagnetic iron oxide (SSPIOs) at 60–150 nm, superparamagnetic iron oxide (USPIO) 5–40 nm,

and ultra-small and monocrystalline iron oxide (MION) 10–30 nm. Magnetic nanosystem is attractive due to its ability to become magnetized after exposure to a magnetic field but does not retain permanent magnetization once the field is turned off. These nanoparticles need to be small so that they can be superparamagnetic in order to avoid agglomeration after stoppage of the magnetic field and remain in circulation without being removed by the immune system [36]. The IO can be degraded to Fe+ ions in the body in the acidic compartments of cells, for example, lysosomes, reducing the potential toxicity of nanoparticles (**Figure 2**). The magnetic flux density and permeability of exterior magnetic fields should be optimized to be strong enough to mediate penetration of nanoparticles across the biological barriers, and provide for sufficient accumulation at target sites while reducing risk to normal tissue [66, 67].

Gold nanoparticles have received attention due to their unique properties. These nanoparticles are easily synthesized and size can be readily controlled by turning the synthesis procedure [68]. These nanoparticle conjugates can exhibit increased targeting rapid transport kinetics, long circulatory half-life, size-enhanced tumor uptake, and biocompatibility. These nanoparticles represent one of the most stable and easily surface functionalized for molecular conjugation [69]. Gold is resistant to oxidation under ambient or physiological conditions, which permits interaction in the biological environment. The shape of gold nanoparticles has been demonstrated to penetrate the cell membrane. When functionalized, they can show increased binding affinity and targeting selectivity with multiple targeting groups as well as tumor selective uptake due to their size [69].

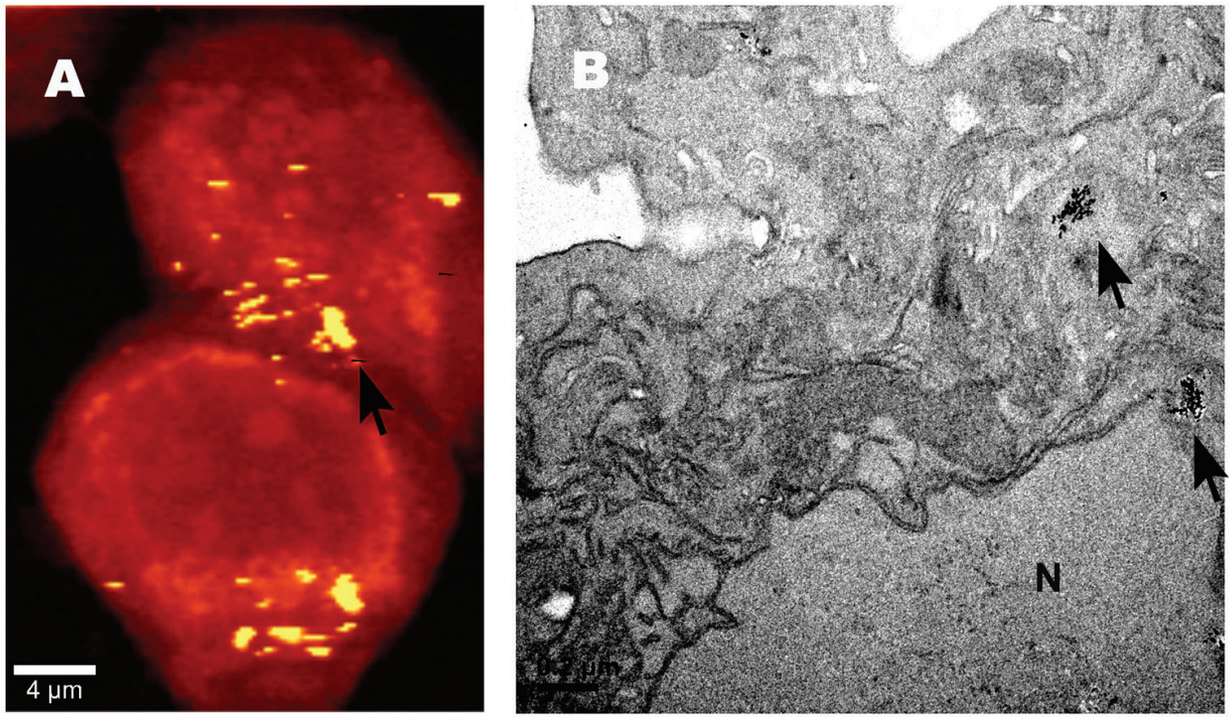

Figure 2. Intracellular occurrence of iron oxide nanoparticles in breast cancer cells analyzed through microscopy. (A) Representative confocal of Raman micrographs after digital contrast enhancement in MDA-MB-231 cells. (B) Ultramicrographs from transmission electronic microscopic (TEM) in MCF-7 are shown. The cells were treated with 200 µM iron oxide nanoparticles at 37°C for 24 and 6 h, respectively. The black arrow denotes accumulation of particles in the cytoplasm of tumor cells.

Inorganic nanocarriers have been used due to their physiochemical properties, such as chemical composition, size, shape, good stability, ease of functionalization, and higher surface-to-volume ratios. Inorganic nanoparticles include gold nanoparticles, magnetic nanomaterials, carbon nanotubes, silica nanoparticles, and quantum dots [49].

4. Tumor targeting and uptake

4.1. Types of targeting agents

Targeting agents can be broadly classified as proteins (mainly antibodies and their fragments), nucleic acids, peptides, aptamers, vitamins, and carbohydrates, and they may be conjugated to the carriers [70]. The surface marker should be overexpressed on target cells relative to normal cells. When targeting agents are used to deliver nanocarriers to cancer cells, it is essential that the agent binds with high selectivity to molecules that are uniquely expressed on the cell surface. Nanocarriers will recognize and bind to target cells through ligand-receptor interactions. The carriers are then internalized and the drug is released inside the cell [71]. The vitamin folic acid (folate) has also been used because folate receptors (FRs) are overexpressed in many tumor cells including kidney, ovarian, and endometrial cancer. The folate receptor is used to deliver drug conjugates to selectively accumulating drugs into cancer cell-mediated endocytosis [72]. One of the more commonly used ligands for cancer cells is transferrin (Tf) protein. Transferrin interacts with Tf receptors (TfRs), which are overexpressed in a range of tumor cells including lung, colon, pancreatic, and bladder cancers to increased metabolic rates [73]. Tf receptors binding directly to nanoparticles such as liposomes have resulted in improved intracellular delivery and therapeutic outcomes in animal tumor models [65, 74, 75]. Studies show that Tf is also used to facilitate small interfering RNAs (siRNA) delivery through transferrin receptors, allowing for antitumor activity [76]. Targeting receptors whose expression correlates with metabolic rate, such as folate and Tf, are also expressed in fast-growing healthy cells such as endothelial, epithelial, and fibroblasts cells, and this could lead to non-specific targeting and may increase toxicity and decrease drug efficiency [77].

4.2. Passive nanoparticle target

Nanoparticles circulating in the bloodstream can reach the neoplastic tissue by passive drug targeting through the enhanced permeation and retention effect (EPR) (**Figure 3**) [45, 78]. When a solid tumor reaches a certain size, the normal vasculature present in its early stage is not sufficient enough to provide the oxygen required for proliferation [79]. Because of this, the cells start to die and they secrete growth factors, which trigger angiogenesis, where budding of new blood vessels from the surrounding capillaries occurs, increasing their permeability. Angiogenesis in tumors is the process of rapid development of new, irregular blood vessels that present a discontinuous epithelium and lack the basal membrane of normal vascular structures [80, 81]. Fenestrations in the capillaries, depending on the location and tumor type, can reach sizes from 200 to 2000 nm. The fenestrations between endothelial cells facilitate the extravasation of nanocarriers from the surrounding vessels into the tumor [82]. The extracellular fluids are constantly drained into the lymphatic vessels, and this allows for the renewal

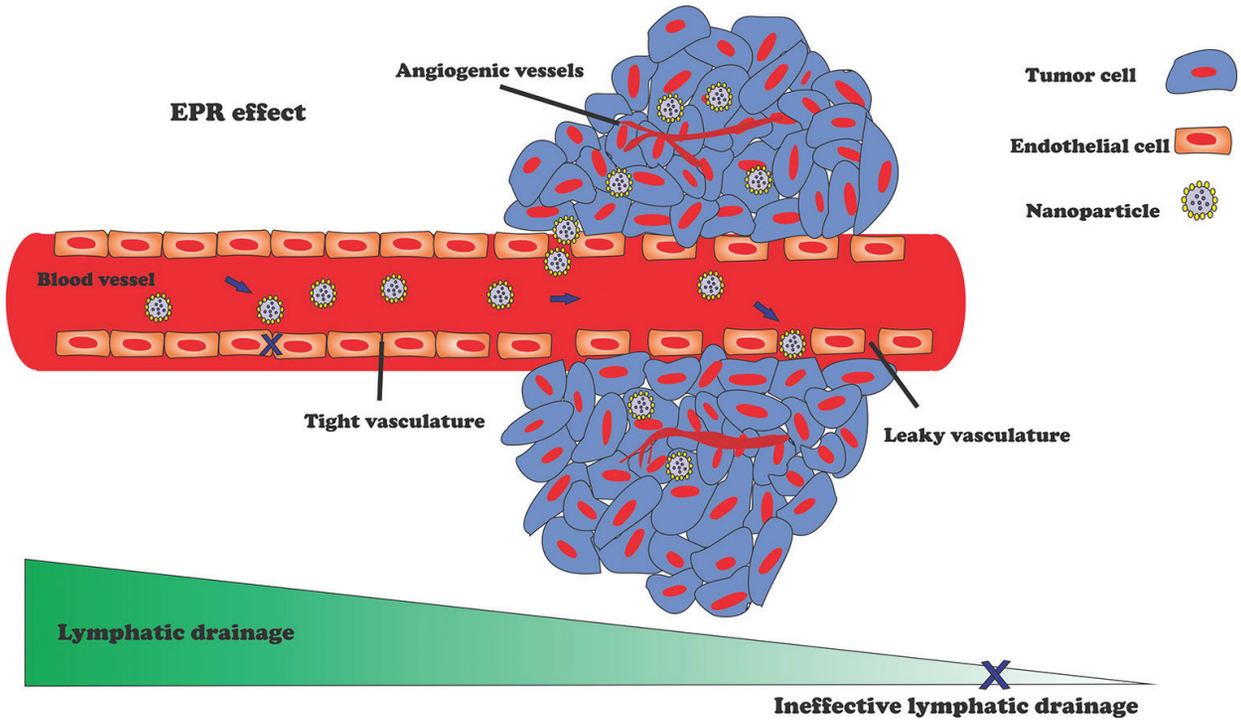

Figure 3. Schematic representation showing enhanced permeability and retention of nanoparticles in tumor.

of interstitial fluid and the recycling of extravagated solutes and colloids back to the circulation [83]. In tumors, the lymphatic function is defective and, consequently, the uptake of the interstitial fluid is minimal [84]. Free drugs may diffuse nonspecifically and a nanocarrier can extravasate into the leaky vessels of tumor tissues through the EPR effect. A study using liposomes of different sizes suggests that particles with a diameter of 200–300 nm are able to extravasate, whereas in another part of the same tumor, molecules only a few nanometers in size may have difficulty entering the interstitium [85]. The success of EPR effect depends on factors such as lymphatic drainage rate, blood flow that is different in various tumor types and degrees of capillary disorder.

4.3. Active nanoparticle target

Passive targeting is available only in certain types of tumors and does not, necessarily, insure internalization of nanocarriers by targeted cells. Nanocarriers can be engineered to attach targeting with selective agents to employ active targeting [86]. As previously described in topic 4.1, some of these agents include peptides [87], proteins [88], antibodies [89], and small organic molecules [90–92]. These agents are complementary to receptors that are overexpressed or present in tumor cells [93]. The objective of passive targeting is to increase interactions between nanoparticles and cells and to enhance internalization of drugs without altering biodistribution [94, 95]. Some physicochemical properties might also affect the efficacy of active targeting *in vitro* and *in vivo*. These properties, such as the size of nanoparticles [96], choice of the targeting ligand [97], and ligand density [98] may affect the efficacy of the active targeting of nanoparticles. The nonspecific biding of proteins during

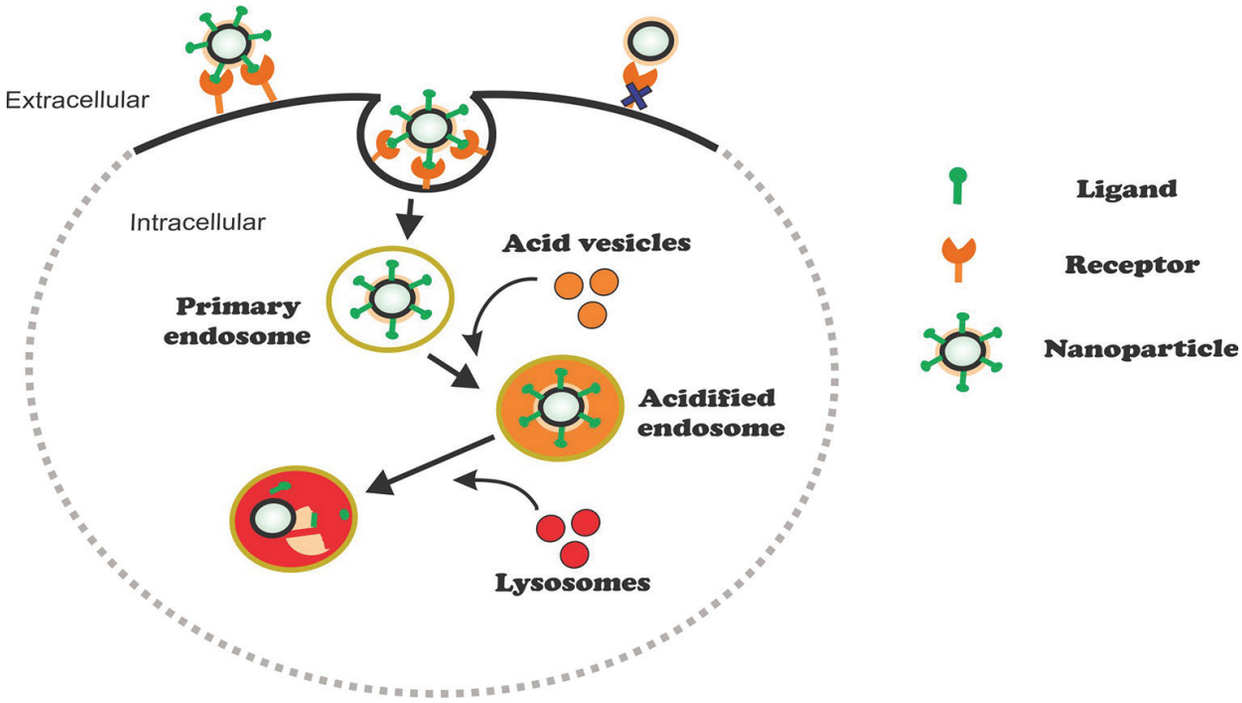

Figure 4. Cellular uptake mechanism. The ligand-coated nanoparticle binds to the membrane receptor, enters the cells by primary endosome, and then forms an acidified endosome. The enzymatic digestion of nanoparticles is done by fusion of lysosomes.

the nanoparticles dislocation through the blood stream and the administration route has been shown to affect the targeting ability of nanocarriers [99]. Active targeting can be used for controlled drug release applications, where the drug is released into the extracellular or intracellular environment. The targeting agents can be used to facilitate nanocarrier internalization into cells, primarily via endocytosis (**Figure 4**) [100].

5. Nanocarriers and multidrug resistance

Multidrug resistance (MDR) limits the potency of many chemotherapeutics can be classified into two types: acquired MDR that can be developed during traditional chemotherapy in common doses and intrinsic MDR that can be developed from preexisting resistance present in tumor cells. MDR is the decreased cell uptake and increased efflux of a drug. MDR transporters carry a variety of anticancer drugs out of cancer cells reducing the intracellular drug doses and produce resistance to chemotherapy [101]. If there is tumor recurrence, chemotherapy may fail because of residual drug-resistant cells dominating the tumor population [5]. Chemotherapy will kill only drug-sensitive cells that do not, or only mildly, express MDR transporters, leaving behind drug-resistant cells that overexpress MDR transporters. The main drug efflux transporters include P-glycoprotein (MDR1 or ABCB1), multidrug resistance-associated proteins (MRP1 or ABCC1), and the breast cancer resistance protein (ABCG2) [102–104]. To combat MDR, stimuli-responsive multifunctional nanoparticle-based drug delivery systems, which can deliver drugs into cells, release the drug in a specific site or

at a specific time. To overcome MDR, an optimal drug delivery system has to release drugs into cytoplasm rapidly and completely, leading to sufficiently high intracellular drug concentration to exceed drug efflux and limit concentration, in order to inhibit the proliferation of drug-resistant cancer cells and kill them. A study done using non-ionic copolymer with a hydrophobic core containing doxorubicin, called SP1049C, has been shown to circumvent p-glycoprotein-mediated drug resistance. The study was done on a mouse model of leukemia and it is currently in clinical evaluation. This study demonstrated the possibility of using nanocarriers to bypass MDR transporters [102, 105–107].

6. Preclinical and clinical trials for nanoparticles breast cancer therapy

The nanomedicine industry perspective toward oncology-based nanomedicinal therapeutics is very promising. The aim of these compounds to improve the therapeutic index of anticancer drugs by modifying their pharmacokinetics and tissue distribution to improve delivery to the site of action is well known and has also been demonstrated clinically. The first anticancer nanomedicine approved by the FDA in 1995, Doxil™/Caelyx™ [108], achieves a differential distribution of doxorubicin versus the free drug and is now approved for several applications, including breast cancer, based upon improved safety with equivalent or superior efficacy versus standard therapies.

Nanomedicines for breast cancer therapy or diagnosis in clinical development can be broadly divided into five main types: liposomes, polymeric conjugates, polymeric nanoparticles, polymeric micelles, and others. Examples of marketed anti-breast cancer nanomedicines and those in clinical development are summarized in **Table 1**.

Nanomedicine type	Drug	Product name/company	Indication	Phase
Liposomes	Doxorubicin	Myocet™/Teva UK	Metastatic Breast Cancer	Approved
	Paclitaxel	LEP—ETU/Insys	Breast cancer	Phase II
		EndoTAG-1/MediGene	Breast cancer	Phase II
Polymeric conjugates	Irinotecan	NKTR102 (PEG)/Nektar	Metastatic breast cancer	Phase III
Polymeric micelles	Paclitaxel	Genexol-PM™/Samyang Biopharmaceuticals	Breast cancer	Approved
	Docetaxel	Genexol-PM™/Samyang Biopharmaceuticals	Breast cancer (NSCLC, prostate, ovarian, head and neck, gastric, and esophageal cancer)	Marketed in South Korea
	Paclitaxel	NK105/NanoCarrier™	Breast cancer	Phase III
Other	Paclitaxel	Abraxane ™/Celgene	Advanced breast cancer	Approved
	Phospholipid stabilized microbubble	SonoVue/Bracco Imaging	Ultrasound enhancement for breast and other cancers	Approved

Table 1. Clinically and preclinical nanoparticle for breast cancer therapies and diagnostics, grouped by their trial phases.

7. Conclusions

The choice of appropriate nanocarriers is a difficult one. It is important to understand the key nanoparticle features such as properties, size, targeting ligand, and charge to improve the design for oncology applications. Nanoparticle therapeutics has been used for many treatments of most cancers. Although the field of nanomedicine is developing rapidly, there are still a limited number of nanocarriers approved by the FDA and limited available clinical data. More clinical trials are required to better understand the advantages and disadvantages of nanoparticle therapeutics. Well-designed studies are important for development of these drugs. Further research is needed to develop new nanotherapeutics incorporating a variety of characteristics along with good experimental design in order to achieve improvements in treatments and nanoparticle targeting to overcome current limitations.

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