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Published in:
SEMINARS IN CANCER BIOLOGY

DOI:
10.1016/j.semcancer.2019.11.002

Published: 01/02/2021

Document Version
Peer-reviewed accepted author manuscript, also known as Final accepted manuscript or Post-print

Please cite the original version:
Raj, S., Khurana, S., Choudhari, R., Kesari, K., Kamal, M. A., Garg, N., Ruokolainen, J., Das, B., & Kumar, D. (2021). Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. *SEMINARS IN CANCER BIOLOGY*, *69*, 166-177. https://doi.org/10.1016/j.semcancer.2019.11.002

Seminars in Cancer Biology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy

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ARTICLE INFO

Keywords:
Cancer
Nanoparticles
Cancer diagnosis
Drug delivery
Cancer therapeutics
Targeted therapy

ABSTRACT

Nanotechnology has been the latest approach for diagnosis and treatment for cancer, which opens up a new alternative therapeutic drug delivery option to treat disease. Nanoparticles (NPs) display a broad role in cancer diagnosis and has various advantages over the other conventional chemotherapeutic drug delivery. NPs possess more specific and efficient drug delivery to the targeted tissue, cell, or organs and minimize the risk of side effects. NPs undergo passive and active mode of drug targets to tumor area with less elimination of the drug from the system. Size and surface characteristics of nanoparticles play a crucial role in modulating nanocarrier efficiency and the biodistribution of chemo drugs in the body. Several types of nanocarriers, such as polymers, dendrimers, liposome-based, and carbon-based, are studied widely in cancer therapy. Although FDA approved very few nanotechnology drugs for cancer therapy, a large number of studies are undergoing for the development of novel nanocarriers for potent cancer therapy. In this review, we discuss the details of the nano-based therapeutics and diagnostics strategies, and the potential use of nanomedicines in cancer therapy and cancer drug delivery.

1. Introduction

Early detection and effective treatment of cancer have been of utmost interest to researchers for decades. With over 3 million hits (and growing) on PubMed and a plethora of diversification, cancer is one of the most widely researched avenues in the field of science and technology today. Healthy cells divide and produce new cells replacing the old ones, thus maintaining the body's steady-state and homeostasis. Cancer originates due to the mutations in the cell, and grows abnormally to form a tumor. Cancer cells metastasize through the blood and lymphatic vessels to different regions of the body, forming tumorigenic mass of cells. Cancer is the second leading cause of death worldwide, causing more than 9 million deaths in 2018 [1].

Early diagnosis of cancer provides the best chance for employing appropriate therapeutic intervention strategies. Efficient early detection of cancer has been often achieved by variety of methods involving tumor markers, imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound scanning, endoscopy, including cytogenetic and cell genetics screening have found applications in the early detection of cancer [1–3]. Recently, a Swedish team led by Tham, recognized the potential of cell-free tumor DNA (ctDNA) as an effective non-invasive strategy for the detection of cancer-associated genetic abnormalities [4,5].

With the advent of a breakthrough in nanotechnology research, it has become relatively more straightforward for researchers and clinicians all around the globe not only to diagnose cancer early, but also to treat the disease effectively. The scientists have been bestowed upon

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https://doi.org/10.1016/j.semcancer.2019.11.002
Received 2 July 2019; Received in revised form 15 October 2019; Accepted 1 November 2019
1044-579X/

with a boon in the name of nanotechnology and nanomedicine that have enabled early and precise diagnosis and effective treatment [6]. Nanodevices such as nano-enabled sensors are being ventured into for their high sensitivity and specificity for the purpose of detection of biomarkers such as cancer-related proteins (either cell surface glycoproteins or secreted proteins), tumor biomarkers (prostate-specific antigen), ctDNA, tumor-shed exosomes, etc. [7]. With growing evidence, nanotechnology has become a favourable tool for early detection and treatment of cancer. A plenty of nanomedicines has been put into use for cancer therapy, such as viral vectors [8], drug conjugates [9], lipid nanocarriers [10], polymer nanocarriers [11], etc. NPs have been proven to be more readily soluble in water, thus increasing the chemical stability and bio-availability of the drug meant to be delivered. Moreover, nanocarriers have the potential to shield the anti-cancer compounds against biodegradation and has a potential to cross blood brain barrier to reach a targeted site. Nanomedicine once again proved its worth due to its advantages such as selective targeting of cancer cells with appropriate ligands [12]. Considering the exponential growth in evidence, nanomedicine, for sure carved a niche for itself in the field of disease diagnosis and therapy. Nanomedicine is among the rapidly growing research avenues and also the most viable option for cancer therapy [13]. In this review, we discuss the potential of nanomedicine as a viable diagnostic and therapeutic strategy for effective management of cancer. Additionally, we also emphasize the important aspects of NPs and its delivery to the specified tissues and organs, and how nanomedicine can be used for targeted drug delivery.

2. Characteristics of nanoparticles

The most efficient way for a nanoparticle to systematically deliver a drug is by remaining in the blood circulation for an extended time period to the target cells and for the constitutive delivery of a drug to the target site [14]. Unmodified conventional drugs are often cleared from the system by the reticuloendothelial system, depending on their size and surface characteristics of the NPs, which are being used for delivery of the drug [15]. Therefore, the nano-drug delivery efficiency can be controlled by modulating their size as well as surface characteristics.

2.1. Particle size

The size of the NPs is considered as a significant characteristics of a carrier system. It determines the *in vivo* distribution, bioavailability, biological fate, cellular toxicity, and targeted delivery through the nanosystem [16]. Nanoparticle size is often manipulated to be big enough to avoid any invasion into blood capillaries and also small enough to escape from macrophages of the reticuloendothelial system and to prevent the elimination of the nanoparticle from the system [17]. The Hanes and his group discovered that a cholesterol-independent, non-clathrin, and non-caveolae mediated pathway that avoids the endo/lysosomal accumulation allows polystyrene particles with a size less than 25 nm to enter HeLa cells [18]. Studies from Levy et al. [16] have reported that gastrointestinal epithelium cell line (caco-2) uptakes 100 nm PLGA particles much faster than their 500 nm - 10 μm counterparts. Also, Pandey et al. [19] had reported that rutin loaded poly (lactic-co-glycolic acid) (PLGA) NPs with lesser particle size improved drug loading capacity and enhanced drug targeting potential and bioavailability. Chan et al. [20] investigated the interactions between SK-BR-3 which is a breast cancer cell line and series of gold NPs coated with Herceptin® with appropriate sizes (2 - 100 nm) and showed that gold NPs with diameter of 40 and 50 nm could enter cells most effectively and have better therapeutic efficacy of Herceptin.

According to the size effect, many studies were done on stimulus-triggering by the nanoparticle or the tumor microenvironment (inner impact by the nanoparticle) to alter the sizes of the nanomedicines. The tumor-penetrating ability of nanoparticle was proven to be inversely proportional to the size of the nanoparticle. For example, Tang et al. revealed that monodispersed 50 nm silica nanoconjugates penetrate into the tumor more efficiently than 200 nm particles [21]. In addition, NPs with a size less than the approximate limiting size, i.e., 200 nm undergoes endocytosis through a mechanism mediated by clathrin shows to have more chances to efficiently cross the blood-brain barrier (BBB) [22]. Also, Chauhan et al. [23] reported particle size with 12 nm can pass into the tumor easier than larger NPs, and both diffusive and convective modes of penetration of 12 nm particles in transvascular and interstitial tissues are faster than that of larger particles. The experiment conducted by Cabral et al. showed that the accumulated efficacy of polymeric micelles with size ranges from 30 to 100 nm in the tumors [24]. Most polymeric micelles can be observed in highly permeable tumors and show anexcellent antitumor efficacy. However, only 30 nm micelles can accumulate in impermeable tumor tissues. Therefore, the initial size of a delivery system should be more significant to achieve more prolonged circulation and selective extravasation, but once “docking” at tumor sites, it should be adaptable to small particles to facilitate effective tumor penetration. Such a demand has encouraged the current generation of stimuli-responsive NPs that are capable of reducing their sizes by responding to enzymes or UV light [25].

2.2. Particle surface characteristics

Along with the size, the surface of NPs equally plays a crucial role in affecting the nanoparticle half-life and fate in the bloodstream [20,21]. The hydrophobic surface of nanocarriers often leads to the opsonization of the nanoparticle delivery system and is cleared by the macrophages in the reticuloendothelial system [26,27]. Surface non-modified nanocarriers often lead to such opsonization events, which fail them to make targeted delivery of the drugs to the site [28]. Consequently, to prolong the nanocarrier circulation in the blood and for the success of targeted delivery of the drug, minimization of opsonization is a crucial factor. This minimization of opsonization can be carried out possibly by involving surface coating of carriers with hydrophilic materials such as polyethylene glycol (PEG) [29,30]. The minimization of opsonization can also be used in constructing nanocarriers from biodegradable block polymers with hydrophilic and hydrophobic domains [23,24]. A study by Alessandro et al. [31] has reported that NanoPorous Silicon particles (NPS) are hybrid particles coated with cellular membranes called LeukoLike Vectors (LLV) are purified from white blood cells were able to prevent immediate clearance of phagocytic cells of the immune system. Also, LLV keeps hold of their functions when injected *in vivo*, showing a good circulation time and accumulation in the tumor. Similarly, a study from Pia et al. (2013), reported that self-peptides delay macrophage-mediated clearance of NPs by specifically binding to the phagocytes, and signals to inhibit the removal of particles as small as viruses and also promotes persistent circulation that enhances dye and drug delivery to tumors [32].

2.3. Particle shape

In addition to size and surface characteristics, the shape of NPs has newly been identified as an important factor that plays a critical role in circulation time, biodistribution, cellular uptake, as well as targeting in cancer drug delivery. The majority of nanocarriers are generated in spherical form, which is mostly developed for anticancer drugs, whereas viruses and bacterial nanocarriers are found in various shapes such as filaments or cylinders [33]. Viruses and bacteria have enhanced their capability to evade the immune response by evolving in non-spherical forms. There is an increasing demand that nanomedicine design should learn from already present biological systems, with the awareness that NPs evolved into nonspherical shapes might display advantageous properties over nanospheres with similar size. Discher et al. have demonstrated through his work the continuous circulation of soft filamentous or worm-like micelles in mice or rats for a week,

thereby demonstrating the importance of nanoparticle shape [34]. The potency of cancer drug delivery is mainly determined by the biodistribution of drugs or drug carriers. The drug has to be delivered to specific biological targets with less systemic biodistribution to maximize therapeutic efficiency. Studies have shown that in mouse xenograft tumors high concentration of filamentous micelles were observed immediately after just 10 min following intravenous (tail vein) administration of near-infrared fluorophore (NIRF) labeled filomicelles into xenograft tumor-bearing mice and the tumors were strongly luminescent in contrast to a relatively weak systemic fluorescent signal [35]. Another study has also observed that PEGylated gold nanorods were distributed in the entire portion of the tumors, whereas gold nanospheres and nanodisks were only found on the surfaces of the tumors [36]. NPs with other nanospherical shapes have shown effective biodistribution. Poly (methyl vinyl ether-co-maleic anhydride)/lipid NPs (GMSLIPO), which are usually irregular in shape has shown to evade macrophages and get localized in the spleen of rats, rabbits, and dogs as compared to spherical carriers bearing the same surface components [37].

There is a considerable number of studies undergoing *in vivo* studies showing the crucial role of nanoparticle shape specifically for cancer drug delivery. Spherical micelles have shown to have less capacity to encapsulate the anticancer drug and also apoptotic efficiency compared with filomicelles [38]. An *in vivo* study on antitumor activity using different micelle shapes revealed that filamentous micelles showed the highest DOX loading capacity and efficiency to encapsulate as well as the broadest therapeutic window for safe dosing and optimum therapeutic effect towards artificial solid tumors [39]. Nanorods with an antibody coating composed of biocompatible PLGA have been reported to release anticancer drugs (e.g., camptothecin) inhibiting breast cancer cell growth [40].

3. Tumor targeting by nanoparticles

The principal aim of targeting cancer cells with chemotherapeutic drugs is to maximize the killing effect on cancer cells and to minimize the side effects [41]. Scientists are in continuous search of developing modifications to several drugs with the help of nanocarriers in selectively targeting the cancer cells. Studies by Chawla & Amiji (2002), have led to the understanding of developing colloidal carriers such as NPs and liposomes for cancer drug delivery [34,36]. Nanoparticles attach or adsorb the drug to their surface, thereby increase the targeting ability of the drug (Fig. 1). Drug targeting using NPs shows several advantages over other delivery systems as NPs can be directed towards the target site using various strategies [42,43]. Also, due to their extremely smaller size these NPs can penetrate easily into rapidly growing tumor mass and can accumulate into the site in large amount making the availability of drug for a longer period to the tumor mass [44]. Nanoparticles have also been widely used to target chemo drugs to lungs as it offers useful and safer means of lung cancer theranostics [45]. Nanosize makes them easily applicable for intravenous, intramuscular, and subcutaneous applications causing less irritation. Targeting tumor cells via NPs involves different strategies, which include active targeting, passive targeting, targeting via nanocarriers such as polymeric, lipid-based, and stimuli sensitive nanocarriers. Rehman et al. (2019) had reported that nano-lipidic carriers loaded with ganoderic acid interacts with various cancer signaling proteins and shows a better tolerant and antitumor efficacy against hepatic carcinoma [46].

3.1. Passive cancer targeting

Passive targeting mainly depends on the tumor's physiological properties, which help in the accumulation of nanoparticle delivery systems similar to micellar systems, liposomes, polymeric-drug conjugates, and polymeric NPs. Rapidly growing tumors with enhanced vascular permeability and defective lymphatic drainage often lead to increased permeability and retention (EPR) effect of the nanosystems in cancer. The significant characteristics of tumor cells showing the EPR effect was first reported by Matsumura and Maeda in 1986, favors for the passive targeting of anti-tumor drugs [47]. This effect, in addition to smaller particles (20–500 nm), also helps in the accumulation of higher molecular weight compounds inside the tumor. Passive targeting is mainly dependent on the nanoparticle size as passive diffusion is achieved by diffusion mediated transport [48]. Nanoparticles within the size range of 40–200 nm provide an extended circulation time, increased accumulation inside tumor mass, and decreased elimination of nanoparticle from the system (Fig. 2). The EPR effect is the major means through more significant compounds with molecular weight more substantial than 50 kDa along with small-sized NPs accumulate specifically in the targeted site [49]. Although the EPR effect overcomes the major dilemma over other conventional chemotherapy of selective targeting of drugs in the tumor site, but moreover the passive targeting via the EPR effect attains an inconsistent accumulation of NPs in the tumor site [50]. Currently large number of NPs are in clinical use such as Genexol-PM™ in Korea and ProLindac™ and Opaxio™ in United States [51]. Also, studies by Awada et al. and Burris et al. have confirmed the

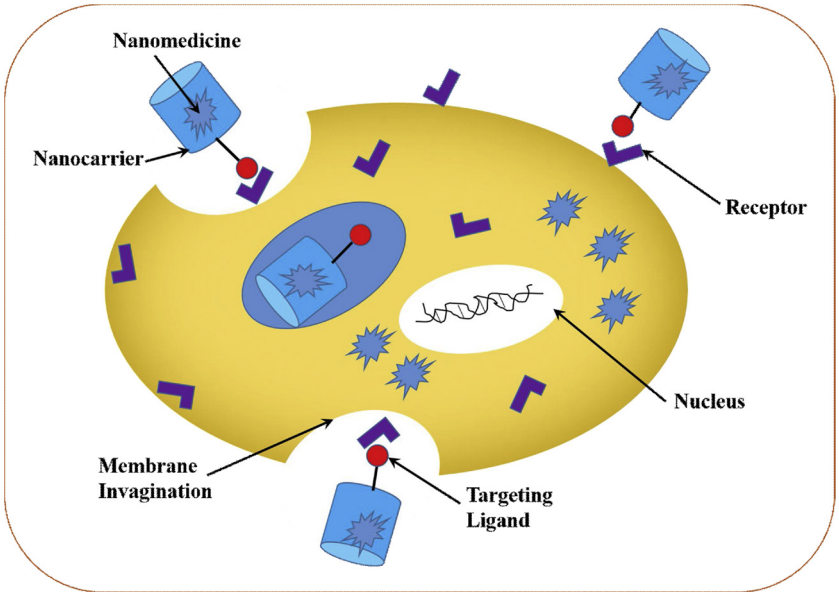

Fig. 1. Internalization of Nanomedicine by the cell. Nanoparticles bind to receptors, which are mostly overexpressed on the surface of cancer cells. Nanoparticles bound to the receptor are self-internalized by the cells, consequently releasing the drug moieties inside the cell. Interestingly, nanoparticles with larger sizes get internalized via endocytic pathways, through which the particles remain trapped in lysosomes and endosomes.

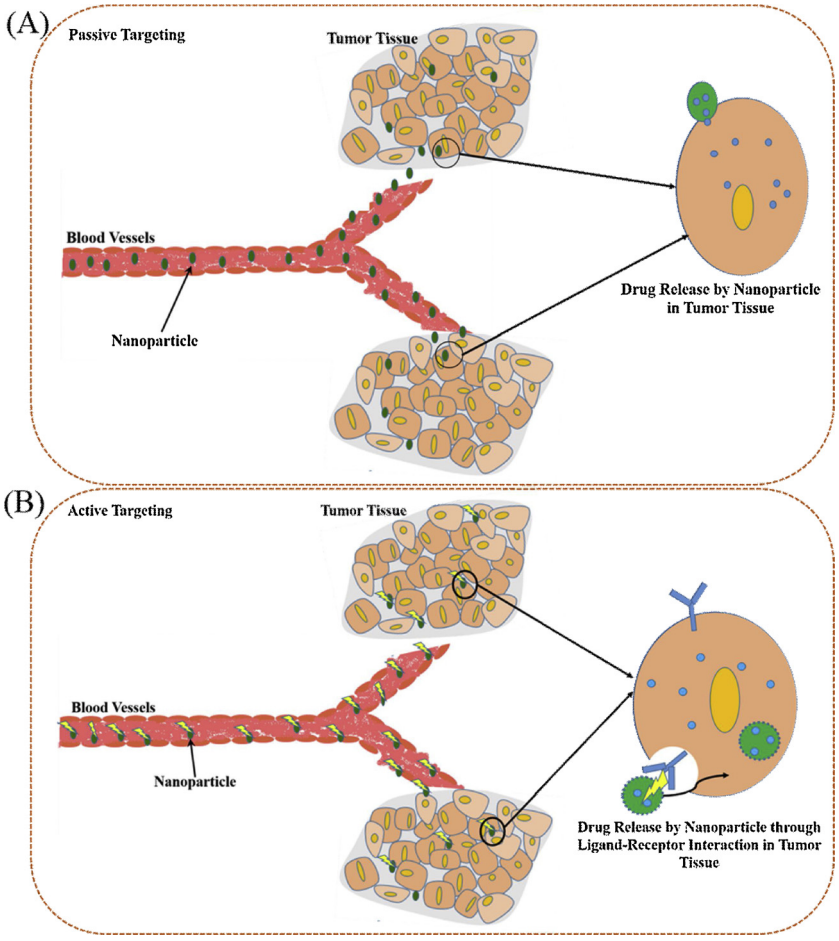

Fig. 2. Mechanisms of tumor targeting by nanoparticles. (A) Passive targeting. Passive targeting is achieved by enabling nano drugs to accumulate in tumor tissues via the unique pathophysiological characteristics of tumor vessels. Typically, tumor vessels are highly disorganized and dilated with a high number of pores, resulting in enlarged gap junctions between endothelial cells and compromised lymphatic drainage. The 'leaky' vascularization, which refers to the EPR effect, allows the migration of nano drugs into the surrounding tumor region. (B) Active targeting. Active targeting enables uptake of nanoparticles through receptor-mediated endocytosis, thereby increasing the therapeutic efficacy and increased accumulation of nanoparticles. Nanoparticles are engineered to incorporate ligands that can bind to endothelial cell surface receptors. In this case, the enhanced permeability and retention effect does not pertain, and the presence of leaky vasculature is not required.

safety and/or therapeutic effectiveness of number of additional nanocarriers, including AZD2811, NK911, and CPX-1 are in clinical investigations [20–22].

3.2. Active cancer targeting

Active cancer-targeting utilizes the attaching targeted moieties for better delivery of nanoparticle systems to the tumor site [55]. Active targeting takes advantage of the highly expressed surface receptors on cancer cells by keeping them engaged with the targeting ligands. The previous study on active targeting of nanoparticle has used an array of ligands from proteins (antibodies), nucleic acids, peptides, or carbohydrates [56]. These ligands can easily attach to the receptors expressed in cancer cells and can mediate the attaching and accumulation of NPs inside the tumor site via receptor-mediated endocytosis then the drug can be released into the site for the therapeutic effect (Fig. 2). The two main factors in determining the efficiency of active targeting are targeting specificity and delivering capacity. The delivering ability of nanoparticle is directly related to the structure and composition of the NPs [57]. The significant challenge for the development of active targeting of NPs is that the required NPs had to be in the vicinity of their target antigen and interact with it. Nanoparticle drug delivery via active targeting is continuously studied for an increase in the efficient capsulation of NPs by the target cells and to prove the efficacy of drug delivery. The study by Kirpotin et al. (2006) has shown that Anti-HER2 targeting moieties on the surface of liposomes highly elevates the capture of the NPs in HER-2 expressing tumor cells [58]. Similarly, Bartlett et al. (2007) showed that delivery of nucleic acids into cells also take advantage of active targeting, as shown with the study that proves to silence a luciferase beacon targeting of transferrin receptor is essential in a neuroblastoma xenograft [59].

Currently, no actively targeted NPs are commercially available, but there are few nanoparticle therapeutics such as liposome targeted and polymeric NPs that are under clinical development stages. MBP-426, MCC-465, SGT53, MM-302, BIND-014, CALAA-01, cetuximad-decorated Doxil/Caelyx liposomes, and a retroviral vector is known to be under phase I/II clinical trials. The epidermal growth factor, Tf-R, PSMA, the surface of gastric cancer cells, and the HER-2 are some of the main therapeutic targets of these NPs [20–22].

4. Targeting via nanocarrier

Nanocarriers play a critical role in specific drug delivery to a particular site. Several nanocarriers have been used for drug tagging and drug packaging (as described in Fig. 3) based on their mode of action. Few important nanocarriers we have discussed in this review, how strategically nanocarriers can be selected for the specific drug delivery targeting particular tissue and organs?

4.1. Self-assembled nanocarriers

The study for polymeric nanostructures has significantly evolved over the year for targeted drug delivery. Polymeric NPs are characterized by self-assembly of amphiphilic block copolymer surfactants such as liposomes, dendrimers, vesicles, emulsion, and latex particles [60]. The advantage of polymeric based nanoparticle targeting is increased tumor toxicity, site-specific targeting of a drug, reduced system toxicity [61]. Moreover, polymeric NPs are easy to compose over other wide range of nanostructures that differ in shape, size, and molecular characteristics. Novel polymeric materials such as metallic organic

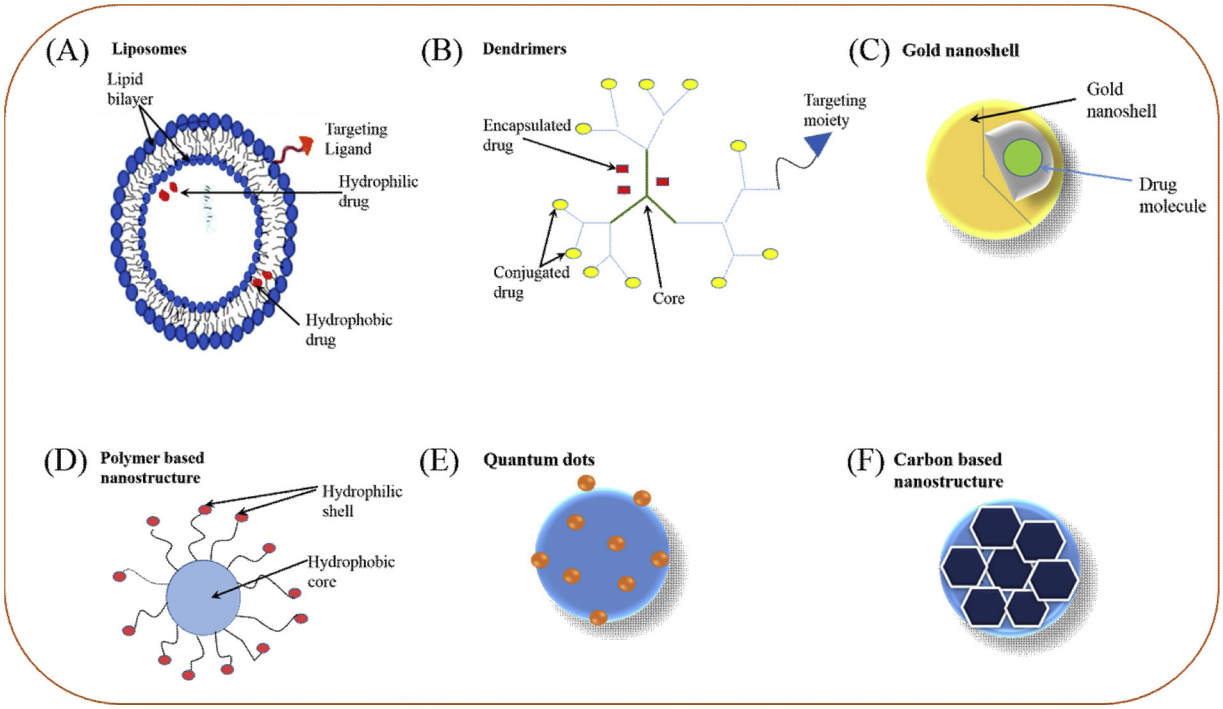

Fig. 3. Different types of nanostructures. (A) Liposomes consist of a hydrophobic region that traps the drug in the central core when liposomes are prepared. The external surface can be functionalized with ligands for active targeting. (B) Dendrimers are usually a series of branched chains where the drugs are carried in the central core of the dendrimers. Dendrimers are linked to targeting moieties for drug delivery to the targeted site. Nanoshells contain small dielectric core surrounded by a thin sheet of metal. (C) Gold nanoshells possess features like optical, chemical, and physical properties, which helps in cancer detection, treatment, and biosensing. (D) Polymersomes are made from polymers encapsulating or trapping the drug on hydrophobic or hydrophilic sites depending on the nature of the drug targeted to tumor tissue. (E) Quantum dots are luminescent nanocrystals having tunable surfaces, making them ideal for optical imaging and detecting various cancer biomarkers. (F) Carbon-based nanostructures are nanosized carbon elements having a diameter less than 100 nm. These particles are created through various methods including carbonization, heating, activation, and grinding.

frameworks (MOFs) posses excellent porosity, high loading capacity, ease of surface modification, among other polymeric materials [62].

4.2. Polymeric micelles

Polymeric micelles are composed of amphiphilic block copolymers, mostly nanoscopic core/shell structures. The hydrophobic core of the micelles acts as a pool for non-water soluble drugs, which helps in the delivery of water-insoluble drugs to the tumor tissue [63]. Seven polymeric micelles based NPs have been in clinical trials under different phases.

4.3. Liposomes

Liposomes are nanocarriers composed of lipid bilayers with a hollow core. The drugs or compounds are embedded in the heart of NPs and delivered to the targeted site [33,34]. Liposomes being a lipid bilayer hydrophilic molecule can be carried in the aqueous interior of the liposomes [64], while hydrophobic particles can be dissolved in liposomes enabling the liposomes to take both hydrophilic and hydrophobic molecules to the target site [65,66]. The mechanism through which liposomes based NPs deliver drug is by fusing liposomes to the lipid bilayer of the cell, enabling the drug delivery to the cytoplasm of the cell. Current progress in liposomes based nanomedicines has widely improved the efficacy and safety of the pharmacotherapy of inflammatory disorders. Also, liposomes have been increasingly explored as one of the efficient systems for delivering a large number of anti-inflammatory drugs, attaining enhanced therapeutic outcomes [67]. Liposomal systems have numerous advantages over drug delivery in both passive and active targeting of drug molecules to the inflammatory lesions [67]. Lipid nanoparticles (LNPs) such as nano-structured lipid carriers, solid lipid nanoparticle, nano lipid-drug conjugates, liposomes, mixed micelles, and nanoemulsions have shown some encouraging results for use in oral anticancer drug delivery through nanotechnological approach [68]. A study by Lee et al. (2009) revealed that for better specific targeted delivery of NPs, liposomes coated with a functionalized polymer, creating a nanobin [69]. Also, studies by Gabizon et al. (1994) has shown that coating liposomes with polyethylene glycol chains (PEGylated liposomes) help liposomes circulate for a longer time improving drug delivery to the targeted site [70]. AmBisome® is a liposome-based delivery system, which is a liposomal formulation of amphotericin B, contains drug dissolved in the lipid bilayer of unilamellar liposomes composed of soy phosphatidylcholine, cholesterol, and distearoyl phosphatidylglycerol. Studies by Moen et al. (2009) showed that AmBisome® had better efficacy and lesser side effects than amphotericin B for the treatment of febrile neutropenia, cryptococcal meningitis, and histoplasmosis [71].

4.4. Dendrimers

Dendrimers are characterized as well defined nanostructures ranging from 1 to 10 nm in diameters. Dendrimers are composed of a series of branched chains around the central core, and the exterior of dendrimers is composed of surface functional groups [72]. The void between the branched chains in the central core can carry the drugs or molecules to target site. Depending on the base structure, different types of dendrimers can be composed, among which, dendrimers consisting of clusters of poly (amidoamine) (PAMAM) units are the most utilized type of dendrimers [73]. Dendrimers deliver the drug to the target site by linking the targeting moiety (sugar moieties involving mannose) to the surface structure such as polypropylenimine dendrimers. Studies by Kumar et al. (2006) showed that the

antituberculosis drug rifampicin was delivered directly to macrophages, and its hemolytic side effects were reduced [74].

4.5. Nanoshells

Nanoshells are NPs that are mostly spherical in a structure that contains a dielectric core enclosed by a thin metallic sheet-like gold [75]. Depending on the use of nanoshells, the shells can be made up of metals as well as oxides that help theNPs in stabilization of colloidal dispersion and also allows modifying particle properties such as optical, magnetic, and catalytic [76]. Due to their optical and chemical properties, nanoshells have been used as biomedical imaging and cancer treatment. The optical properties of the particle are susceptible to the core to outer shell ratio. Nanoshells can be made useful for biological applications by manipulating their geometry and material properties [77]. Nanoshells contain a quasiparticle known as plasmon and possess specific optical properties, which is a group excitation of quantum plasma oscillation, where the electrons simultaneously oscillate with respect to all the ions [78]. Gold nanoshells are used in cancer detection, treatment, and medical biosensing with the help of their attractive set of optical, chemical, and physical properties [79]. The conjugation of gold nanoshells with conventional therapies has reduced its side effect as the gold nanoshells provide enormous sensitivity, throughput, and flexibility to increase the quality life of patients.

4.6. Quantum dots

Quantum dots are being widely studied as a newly discovered probe for biomedical imaging in both *in vitro* and *in vivo* due to their distinctive optical and electronic characteristics [80]. Quantum dots based probes show high specificity and sensitivity to target cancer molecules when conjugated with biomolecular agents such as antibodies, peptides, or other small molecules. Quantum based biomedical imaging helps in understanding the tempo-spatial relationship among molecules by simultaneously staining several biomarkers [81]. Studies by Tholouli et al. (2008) revealed that biomolecular imaging by quantum dots helps in deciphering the molecular mechanism of cancer invasion and is useful in studying tumor microenvironment [82]. Gao et al. (2004) demonstrated a classic example of cancer detection by labeling human prostate cancer cells with quantum dots conjugated with an antibody with prostate-specific membrane antigen (PSMA) [83]. Quantum dots being highly stable of their fluorescence imaging are being highly studied to label intracellular compartments. Quantum dots have been used to label endosomal compartments, f-actin filaments, mortalin, and p-glycoprotein [84]. The use of quantum dots for imaging in human disease, however, is limited by their potential heavy metal toxicity.

4.7. Viral nanocarriers

Viruses are well known for their ability to infect the host and deliver their genetic material very efficiently. Therefore, viruses are highly considered as an excellent source for drug delivery. According to the study by Singh et al. (2007), viral carriers usually derived from plants and bacteria were biocompatible and biodegradable as well as non-toxic and non-infectious in humans and other mammals [85]. A study by Steinmetz et al. (2009) showed that the cow pea mosaic virus (CPMV), a viral nanoparticle has a natural affinity to endothelial cells [86]. Consequently, CMPV act as a natural endothelial probe for imaging vascular cells [87]. So, their natural ability target cells for genome delivery is widely studied and hopes to be a novel way of targeting cancer cells for specific drug delivery.

4.8. Carbon carriers

Carbon nanotubes are rolled-up like tubular structures composed of benzene rings lying under the fullerene structure family [88]. Carbon nanotubes based upon their nanometric dimensions have been categorized into two groups, i.e., single-walled nanotubes (SWNT) composed of one layer of cylinder graphene and multi-walled nanotubes (MWNT) consisting of multiple concentric graphene layers. Carbon nanotubes are considered as suitable carriers in drug delivery because of 'their properties like organized structure, ultralight weight, high electrical and thermal conductivity, and also due to its more top surface area [89]. Carbon nanotubes have been used in the production of biosensors for diagnosis of genetic disorders or other molecular abnormalities, and also in drug delivery systems for a broad range of detection and therapeutic agents. Although a relatively new drug carrier, graphene nanocomposites has been widely explored as an efficient chemotherapeutic carrier and theranostic because of its numerous physicochemical properties, including the capability of multiple payloads, functionalization for drug targeting and photothermal effect [90]. Despite potential benefits, its translation from bench to bedside in cancer therapy is challenged due to its toxicity concern [5,59]. The study by Yan et al. (2014) had reported that carbon nanotubes, when injected into tissues around the tumor, showed no toxic side effects in the human body, thus making the carbon nanoparticle a promising nanoparticle for the specific delivery of the drugs to the tumor tissues [91].

5. Nanomedicines in cancer therapy

Treatment and diagnosis of cancer by anticipating nanomedicines are largely still under the developmental phase. Nanotechnology in the field of medicine includes the use of precisely engineered materials for the innovation of novel therapies and devices that reduces toxicity, and increase efficacy in specific targeting of drugs inside the tumor tissue, compared to the conventional chemotherapies. Abraxane and Doxil are the first nanotechnology-based drugs that have passed the regulatory scrutiny and are already available in the market [52,53]. There are NPs that are FDA approved as well as in clinical trials for different types of cancer therapy (Table 1).

6. Tissue-specific nano-drug targeting

Rapid growth of nanomedicine makes good use of nanotechnology in the field of biomedical sciences. Nano drug formulations have a multitude of advantages such as improved solubility, enhanced efficacy, less toxicity, increased selectivity for tissues, and also can cross the blood-brain barrier. Nano drugs are basically existing standard drugs, conjugated to the NPs to ensure improved pharmacokinetic and pharmacodynamic properties and effective treatment outcomes. It is crucial to understand the target region while designing nano drugs. Delivery of nano drugs has been categorized in mainly as passive targeting and active targeting. Passive targeting is achieved through localization of NPs into specific organs via mechanisms such as the reticuloendothelial system (RES), or efficient permeability and retention (EPR) system. Active targeting involves conjugation on the periphery to ensure the enhanced delivery of NPs. In order to achieve active targeting, i.e., tissue specificity, ligands such as proteins, antibodies, or small biomolecules are attached to the surface of the drug-NP conjugate, thus increasing the intracellular drug accumulation and cellular uptake of the target tissue. A recent review by Ventola described in detail the potential use of different types of approved nano drugs such as Liposomal NPs, Polymer NPs, Micelle NPs, Nanocrystal NPs, Inorganic NPs, Dendrimer NPs, etc. [94]. The advantage of active targeting compared to passive targeting is the selective delivery of NPs to specific tissues, remains for a more extended period of time at the site of infection, thereby increasing NP accumulation. Another approach has been put to good use in the last few years is pHLIP technology, which involves the use of a membrane peptide that senses acidity at the surface of the cancer cells [95]. There are still several obstacles for targeted nano-delivery systems to overcome. The problems of NP stability, size uniformity, and sterility at a larger scale have yet to be addressed and *in*

Table 1
Nanoparticles based drug approved by FDA. Ref [54,56–58].

Generic name and/or Proprietary name	Nanotechnology platform	Active pharmaceutical ingredients	Cancer type	Status
Abraxane	Nanoparticle bound albumin	Paclitaxel	Breast cancer, Pancreatic cancer, Non-small-cell lung cancer	Approved by FDA
DepoCyt	Liposome	Cytarabin	HIV-related Kaposi sarcoma	Approved by FDA
DoxorubiLiposomalcin (Doxil)	Pegylated liposome	Doxorubicin	HIV-related Kaposi sarcoma, ovarian cancer, and multiple myeloma	Approved by FDA
Liposomal daunorubicin (DaunoXome)	Liposome	Daunorubicin	HIV-related Kaposi sarcoma	Approved by FDA
Liposomal doxorubicin (Myocet)	Liposome	Doxorubicin	Metastatic breast cancer	Approved in Europe and Canada
Liposomal irinotecan (Onivyde or MM-398)	Pegylated Liposome	Irinotecan	Post-gemcitabine metastatic pancreatic cancer	Approved by FDA
Liposomal vincristine (Marqibo)	Liposome	Vincristine Sulfate	Acute lymphoblastic leukemia	Approved by FDA
Mifamurtide (Mepact)	Liposome	Muramyl tripeptide phosphatidylethanolamine	Nonmetastatic, resectable osteosarcoma	Approved in Europe
Nab-paclitaxel (Abraxane)	Albumin NP	Paclitaxel	Breast, lung and pancreatic cancer	Approved by FDA
Nab-rapamycin (ABI-009)	Albumin NP	Rapamycin	Advanced malignant PEComa and advanced cancer with mTOR mutations	Phase II
Nanotherm	Iron oxide nanoparticle		Thermal ablation glioblastoma	Approved by FDA
Oncaspar	Polymer protein conjugate	L-asparaginase	Leukemia	Approved by FDA
Onivyde	Liposome	Irinotecan	Pancreatic cancer	Approved in Europe and Canada
Paclitaxel (Genexol-PM)	Polymeric micelle	Paclitaxel	Breast cancer and NSCLC	Approved in Korea
ThermoDox	Liposome	Doxorubicin	Hepatocellular carcinoma	Phase III

vitro and *in vivo* validation on animal models.

7. Cell-specific nano-drug targeting

The evolution of nanoparticle-based drug delivery is catching all the attention due to its uniqueness in biomedical applications and tumor targeting. Using NPs depends on their ability to accumulate in desired cells or tissues. Studies have demonstrated the application of NPs as drug delivery vehicles in chemotherapy. For instance, recently, the American team led by Nima et al. demonstrated the potentiality of nano-drug delivery (doxorubicin) to breast cancer and prostate cancer cells using silver decorated gold nanorods [96]. Also, another study showed the tremendous potential of NPs conducted by Carregal-Romero et al. emphasizing on the use of iron oxide-based NPs that released the drug under the influence of magnetic fields [97]. Curcumin, which is commonly found in turmeric, has been known for long to have anticancer properties but known to have poor bioavailability. Encapsulating curcumin polymorphic NPs resulting in 'nano curcumin' has improved its solubility and bioavailability. This nano curcumin has been seen to mimic the action of free curcumin in pancreatic cancer cells and highly effective in inducing apoptosis, blockade of nuclear factor kappa B activation (NF-κB), and suppression of pro-inflammatory cytokines like IL-6, Il-8 and TNF-α [98], which are often upregulated in various cancer and contribute towards tumor promotion and progression. Another promising application of NPs has been seen in the form of quantum dots; further, NPs conjugated to epidermal growth factor type 2 receptor (EGFR2) monoclonal antibody achieved therapeutic efficacy in targeting tumors [99]. Since the dawn of nanotechnology, biomedical applications of nanoparticle-based drug deliveries have seen tremendous growth, bringing a new ray of hope for developing effective targeted therapeutic intervention strategies in treating ever-evolving cancer.

8. Organ based drug delivery

Specific targeting of drugs using NPs has been broadly studied on tissue and organ level. Drug delivery by nanoparticle is considered to be successful if the delivery of the drug is achieved at the target site with less toxic effect without affecting surrounding normal tissues [100]. Nanoparticles are mostly designed on the basis of route of drug delivery and target tissues so as to get more resident time and availability of drugs in the target site. Nanoparticles are designed in a manner, so that specific tumor can be targetd in a complex human organ system. Drug targeting in organs such as lung has been widely studied via carriers conjugated with targeting ligand such as arginine–glycine–aspartate (RGD) or antibodies that recognize the surface markers of the lung endothelium [101]. Similarly, drug targeting in the liver is achieved by both active and passive targeting. Particle size below 80 nm, essentially reach to the liver cells through targeted drug delivery via passive targeting. Whereas, through active targeting ligand guided drug carriers predominantly help in targeting the liver cells [102]. The kidney is another organ that uses targeting strategy by size-controlled drug carriers and prodrug approaches for drug delivery [103]. Immunoliposomes, which are antibody carrier conjugates, have been widely explored for targeting drugs to the kidney. The brain is an important organ in human, possess considerable challenges in taking up drugs in treating brain diseases. The blood-brain barrier (BBB) tightly regulates the entry of substances to the brain, which makes the drug delivery process difficult [104]. Several strategies have been approached for drug delivery into the brains, such as direct injection of drug into brain [105]. Nanoparticle drug delivery through active targeting involves the modification of drug or drug carriers to facilitate drug delivery through blood-brain barrier. During the last few decades several novel drug delivery systems are already in market and have been developed using various nanomaterials. To achieve the controlled and targeted delivery of drugs nanotechnology modifies many of its properties such as the

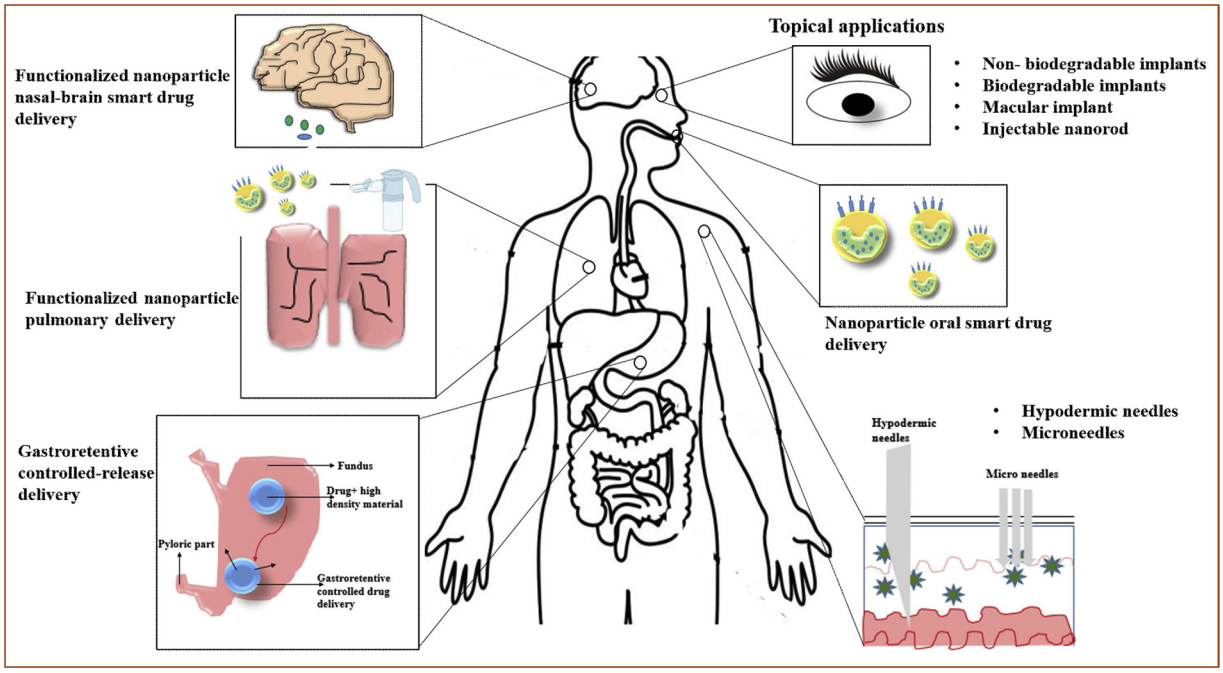

Fig. 4. Various significant routes of nano-drug administration and targeting strategies. The figure depicts the enormous applications of new nanomaterials for the development of different ways of administration and targeting for therapeutics such as transdermal vaccine delivery, intranasal vaccine delivery, and lung targeted delivery. Nasal mucosa offers numerous benefits as a target tissue for drug delivery, particularly for brain targeting because of drug penetration through the cells-free barrier favor lipophilicity.

size and other physical characteristics [106]. The bio-adaptability and multi-functional properties of smart delivery system reduce the toxicity of drugs in different routes of administration, including rectal, nasal, ocular, oral, topical route such as transdermal, and dermal, parenteral route such as intravenous/intravascular, intramuscular, subcutaneous, intradermal/intracutaneous, intraperitoneal and intrathecal (Fig. 4). Specifically, the intranasal delivery which is non-invasive gives a huge interest in the targeted route of administration. Nasal delivery helps drugs to bypass the blood-brain barrier and acts as an efficient platform for brain targeting [107]. The nasal route serves as a major route for local delivery, nasal vaccines, systemic delivery and CNS delivery for drug administration to treat different diseases. As the nasal mucosa involves abundant nasal associated lymphoid tissue (NALT), dendritic cells, large surface area, and low proteolytic enzymes that act as a primary defense system against pathogens, the nasal vaccination act as an efficient alternative to the classic parenteral route [108]. It can show high drug concentration, permeation, no first-pass effect and compliance administration without enzymatic destruction. Moreover, NPs that are encapsulated inside antigens show enhanced uptake and controlled release of antigens from the nasal vasculature membrane with strong immunogenicity and improved systemic therapeutic responses [109]. Also, the bio-nanotechnology is applied to the parenteral administration techniques such as microneedles, jet-injections, ultrasound, iontophoresis, and electrophoresis. In contrast to the painful injection mode of drug delivery these systems provide painless, patient-friendly alternatives for the delivery of molecule [110]. Microneedles are arrays of micrometer-sized shallow needles that penetrate only into the superficial layers of skin which reduces the pain involved with standard hypodermic needles [111]. Microneedles have been made from polymers have been shown to be more effective than different other materials. They have also been developed in solid and as well as in hollow forms. Solid microneedles are used to make skin permeable, while the hollow microneedles actively deliver drugs at a controlled rate into the skin. These new routes of administration of therapeutics with improved responses have been achieved by high drug concentration in target, permeation, no first-pass effect, high bioavailability and compliance administration without enzymatic destruction [112].

9. Nanoparticles in cancer diagnosis

During the last decades, a wide range of NPs has been developed and evaluated for their efficient application as diagnostic and therapeutic agents [113]. Currently, *in vivo,* molecular imaging involves a major focus area of medical research. The rapidly evolving field of molecular imaging has led in faster and easy ways of early disease diagnosis and disease staging and enables image-guided therapy and treatment personalization [113]. Nanoparticles, as contrast agents for functional and molecular imaging [114], include polymers, liposomes, ultrasmall superparamagnetic iron oxide (USPIO) NPs [115], and gold NPs [92,93]. The early detection demands on NPs depend on a rapid and highly site-specific contrast enhancement. Imaging of tumor angiogenesis and vascularization is a reasonable indication for nanoparticle contrast agents [116]. For an increased permeability and retention (EPR), non-targeted nanoparticle formulations are being used, while the targeted nanoparticle formulations binding to activated and proliferating endothelial cells are utilized to detect tumor malignancy and aggressiveness also to characterize mechanistic changes in tumor vascularization, such as vessel maturation during anti-angiogenic therapy or vascular inflammation during radiotherapy. Nanoparticles can detect the presence of cancer-specific genetic mutations or the functional characteristics of tumor cells when they are being produced to act as molecular imaging agents [117]. Some of the NPs known as bioactivatable nanoparticles change their properties in response to factors or processes within the body and act as dynamic reporters of *in vivo* states, thereby providing both spatial and temporal information on disease progression and therapeutic intervention. This information can be used to choose a treatment course or alter a therapeutic plan.

10. Side effects/toxicity of nanoparticles in cancer therapy

Nanotechnology is being advanced and more targeted treatment approach to cure various diseases, including dreadful disease cancer

[118]. The nanomaterials have the ability to be used as targeted therapeutics to specific sites of a disease, which helps in the reduction of off-target toxicity of many drugs. In contrast to the beneficial outcomes, the usage of NPs for drug delivery also raises various safety concerns. Many nanomaterials are synthesized as commercial products and are introduced into our daily lives, such as zinc oxide nanoparticles, titanium oxide nanoparticles [119–121]. Certain NPs can lead to inflammation and fibrosis, resulting in phagolysosomal membrane permeability, the formation of reactive oxygen species, and activation of NLRP3 inflammasome [122]. The smaller the size of nanoparticle, larger is the surface area that can expose more surface molecules to cellular components. Various formulations have been used for drug delivery purposes, including albumin, poly(D,L-lactic-co-glycolide)acid (PLGA), solid lipid formulations, cetyl alcohol/polysorbate NPs, hydrogels, gold, magnetic iron oxide, etc [123,124]. The properties of nanomaterials make it challenging to know how they will penetrate into various biological barriers or metabolize, which makes it difficult to understand their biodistribution and toxicity. Nanostructures can distribute to multiple organs as intact NPs, or metabolizeinto multiple pieces, which can facilitate the cells to different organs and accumulate in them for an unknown amount of time before being excreted from the body [125,126]. Nanostructures are known to have electronic, optical and magnetic properties. The breakdown of these nanostructures could lead to unique toxic effect that is difficult to predict [127]. Nanoparticles that are loaded with anti-tumor drugs that would target organ and cells of interest but their fate in the body system is not known. Studies from Wang et al. (2010) have reported that NPs without any drug formulations possessed the ability to induce cell death in certain types of cells [128]. Small-sized magnetic NPs with high reactivity and great capacity could become potentially lethal factors by causing adverse cellular toxicity and harmful effects, unusual in micron-sized counterparts. Studies have also shown that NPs can exert certain toxic effects when they enter into the organisms during ingestion or inhalation and also can translocate within the body to various organs and tissues [129]. One of the nanoparticle toxicity is the ability to accumulate around the protein concentration depending on particles size, curvature, shape and surface characteristics charge, functionalized groups, and free energy and can generate some toxic effects through protein unfolding, fibrillation, thiol crosslinking, and loss of enzymatic activity [130]. The production of carbon nanotubes (CNTs) and graphene oxide is becoming commercially important although it has been reported that CNTs and graphene oxide are toxic [131,132].

Biodegradable nanoparticles (NPs) are colloidal particles with a gene of interest encapsulated inside a polymeric matrix [133]. These are mainly formulated using FDA-approved biodegradable, biocompatible polymers such as poly(D,L-lactide-co-glycolide) (PLGA) or polylactide (PLA) and are mainly of 100 nm in diameter [133]. The NPs having encapsulated plasmid DNA entrapped are taken up by cells through an endocytic process and are being protected from degradation by both extra- and intracellular nucleases [134]. It is released slowly, sustaining gene delivery and gene expression. Lipid- or polymer-based complexes show a higher transient gene expression where most of the delivered DNA is available quickly for transfection. Biodegradable or polymeric NPs have the potential to be used in targeted drug delivery in cancer chemotherapy. Various molecules are being employed for the nanoparticle to develop nanomedicine providing sustained release and excellent biocompatibility with cells and tissues [135]. In addition, they have the ability to be highly used in encapsulation of peptides, nucleic acids, and proteins. They are also considered as non-toxic, non-immunologic, non-inflammatory, and do not activate neutrophils. Poly-(D,L-lactide-co-glycolide) has been used very successfully as a nanosystem for targeted delivery of drugs and other molecules [136]. As, poly -(D,L-lactide-co-glycolide)-based nanosystem undergoes hydrolysis and produce biocompatible metabolites, lactic acid, and glycolic acid, they have been reported to be least toxic to biological systems. However, there has been recently published one report proposing that surface coating induces the toxicity of polymeric NPs towards human-like macrophages [136].

Most of the metal-based NPs are non-biodegradable. Metal-based nanoparticles (NPs) are a leading class of NPs developed for their functions as semiconductors, electroluminescent, and thermoelectric materials [137]. With the current demand in the development of nanotechnology, many studies have been performed to check whether the unique characteristics of these NPs, such as their large surface area to volume ratio, might have a negative effect on the environment. Researchers have since found that many metal and metal oxide NPs have deleterious effects on the cells with which they come into contact involving DNA breakage and oxidation, mutations, reduced cell viability, warped morphology, induced apoptosis, and necrosis, and decreased proliferation [138].

One review proposes that the evidence collected since the discovery of fullerenes completely points to C_{60} being non-toxic [139]. Aluminum-based NPs which is another kind of non-biodegradable nanoparticle have wide application in areas such as fuel cells, polymers, paints, coatings, textiles, biomaterials, etc., Chen et al. have reported about their toxic effects mentioning that aluminum oxide NPs alter the cell viability, alter mitochondrial function, increase oxidative stress, and also alter tight junction protein expression of the blood-brain barrier (BBB) [140]. Gold NPs have unique physical and chemical properties. They have the capability of easy functionalization, binding to amine and thiol groups [141]. Due to the possession of all these characteristics acquired by gold NPs are investigated as drug carriers in cancer and thermal therapy. Gold NPs are considered to be relatively safe, as its core is inert and non-toxic [142]. However, reports alsosuggest that the cytotoxicity of gold particles is associated with the side chain (cationic) and the stabilizer used [143]. Cytotoxicity of gold NPs is dependent on the type of toxicity assay, cell line, and physical/chemical properties. The difference in toxicity profile for different cell lines is observed in human lung and liver cancer cell lines. The toxicology studies on mice as of 2013 involving exposure to carbon nanotubes (CNT) showed a limited pulmonary inflammatory potential of MWCNT at levels corresponding to the average inhalable elemental carbon concentrations observed in U.S.-based CNT facilities [144]. The study estimated that considerable years of exposure are necessary for significant pathology to occur.

Though NPs are useful for a variety of applications, still there exist health hazard concerns due to their unregulated use and discharge to a natural environment. Therefore, there is a need to make the use of NPs safer and environmentally friendly.

11. Challenges of nanomedicine in cancer therapeutics

Nanomedicine has emerged as a highly promising tool for cancer therapeutics and has proven to be advantageous over conventional therapeutic strategies. Despite the enormous applications and benefits, nanomedicine is not free from limitations. With a drastic reduction in the size of the NPs, the number of particles increases, further rising the inter-particular friction. With increased surface area, the chemical reactivity of these particles tends to increase the chemical reactivity resulting in excessive production of reactive oxygen species (ROS) further responsible for oxidative stress, inflammation, damage to DNA, and proteins, thereby causing gene toxicity. Oxidative stress can also cause neurodegenerative disorders such as Alzheimer's or Parkinson's disease. Another drawback with the use of NPs is the occurrence of unforeseen interactions of NPs inside the body resulting in unanticipated consequences such as undesirable entrance into the blood-brain barrier (BBB). Moreover, selective targeting is also a challenge in itself. It is well known that surface proteins found in normal cells are overexpressed in most cancers, which does not guarantee selectivity. There is a need for the selection of effective and appropriate targeting ligands for selective targeting of tumors. There is a very high chance of the drug going off-target and affecting the normal healthy cells. Another cause of

worry is the manufacturing of nano drugs. Large scale synthesis of nanomedicines is still an obstacle [145]. Overcoming these obstacles may currently seem like an arduous task, but targeted effort can make it possible. New invention in cancer research has seen significant advancement in treating disease. Nanomedicine is considered as an alternative technology to overcome the gaps. Thus, it provides lot of scope and challenge for researchers all around the globe.

12. Conclusions and future perspectives

Nanomedicine is explored by researchers across the world as a potential approach for drug delivery and effective therapeutics. In cancer research, nanomedicine holds the massive potential for cancer therapy. The surface and tiny size and shape of NPs have been used as unique properties of NPs to play a key role for an efficient treatment and targeting. Nano based therapeutic and diagnostic strategies pose as highly promising tools for easy and cost-effective diagnosis of cancer. In all likelihood, with the help of the advancing knowledge in molecular medicine, immunology, biochemistry, and artificial intelligence, nanomedicine will be the future of the most efficient diagnosis, treatment, and management of cancer. The evolving of nanomedicine has shown to be a novel and promising alternative technology over conventional cancer therapies and provides new opportunities for early diagnosis, improved treatment of cancer. Although nanomedicines have the capability of delivering cancer-targeting agents with lower systemic toxicity, it is of great importance to consider the cancer complexity and dynamics for bridging the translational bench-to-bedside gap. It is important to do more investigations for exploiting the tumor microenvironment, and achieving a more comprehensive understanding of the fundamental biological processes in cancer and their roles in modulating nanoparticle–protein interactions, blood circulation, and tumor penetration.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

We thank our lab members and colleagues for carefully reading the manuscript and contributing valuable inputs for improving the manuscript. S.R. and D.K. were supported by the Department of Science and Technology-Science and Engineering Research Board (DST-SERB) funded research grant (ECR/2016/001489), Government of India, India.

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