Utility of Nanomedicine for Cancer Treatment

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Abstract

The conventionally available cancer therapies present intrinsic limits which have prompted the development and application of nanotechnology which offer a promising effective and safer treatment. This has resulted in the development of cancer nanomedicine which has allowed researchers to improve techniques for delivering chemotherapeutic agents precisely at the molecular level in tumor tissues. This entails the use of nano-scale objects themselves or part of larger devices containing multiple nano-scale objects. Recently, most Bioscience fields use nanotechnology which has the impact on biomedicine and has potential to change the conventional cancer diagnosis and treatment. Commercial trials have begun on nano-based cancer therapies and diagnosis, however, others are still under development. Today, cytotoxic drugs can be efficiently delivered to tumor tissues using nanocarriers like nanoparticles which depend on difficult concepts of pharmacology. Multiple drugs can also be developed at the cancer site using nanomedicine which presents better cytotoxic effects. Nanomedicine also presents a targeted chemotherapeutic method under cytImmune science which is still a developing field. This field enables the selective delivery of drugs at the cancer site, due to increased permeability of the blood vessels at the tumor sites. In our review, we focused on the anticancer nanomedicine scope.

Keywords: Nanomedicine; Nanotechnology; Cancer therapy; Pharmacology; Nanoparticles

Introduction

Conventional cancer therapies cause damage to healthy tissues or incomplete eradication of cancer and these are limited to surgery, radiation, and chemotherapy. Lack of aqueous solubility of the drugs, multi-drug resistance developed after repeated administration of the same drug and lack of selectivity for the cancer cells are some of the limitations observed in conventional cancer therapy [1]. Nanotherapeutics has taken the center stage in cancer research and is directed towards solving many limitations that face conventional cancer therapy. The nonspecific target of cancer chemotherapy leads to damage rapidly proliferating normal cells [2]. These adverse effects can be significantly reduced through the administration folate and transferrin-mediated nanotherapeutics which are aimed to target cancerous cells. Solid lipid nanoparticles (NPs), mesoporous silica NPs, nanoparticulated chemosensitizer, nanoparticulated poloxamer, polymeric NPs, and magnetic NPs are being developed to reduce multidrug resistance which is a great challenge in cancer therapy. Poor aqueous solubility and low bioavailability are caused by chemotherapeutic drugs which are hydrophobic [3].

Nanocrystals, albumin-based NPs, liposomal formulation, polymeric micelles, cyclodextrin and chitosan-based NPs help to overcome these challenges. The use of nanotechnology-based therapeutic agents leads to a decreased risk to the patient and an improved survival rate. The possibility of destroying cancer tissues with minimal damage to healthy tissue and organs, detection of cancer and elimination of cancer cells before they form tumors has increased due to the use of nanotechnology [4]. The field of chemotherapy is integrating with NPs to deliver multiple chemotherapeutic agents on different targets but a non-conventional dosing is the way to go. Different patients have different medical conditions and phenotypic personalized medicines are required. An arbitrary dosing scenario is a great risk in these issues creating a parameter space that is too large

to be individually tested. Along with enormous progress in the field of cancer nanomedicine (Figure 1), many challenges and opportunities lie ahead. Careful patient selection is required to identify those most likely to benefit from a given nanotherapy due to the complexity and heterogeneity of tumors.
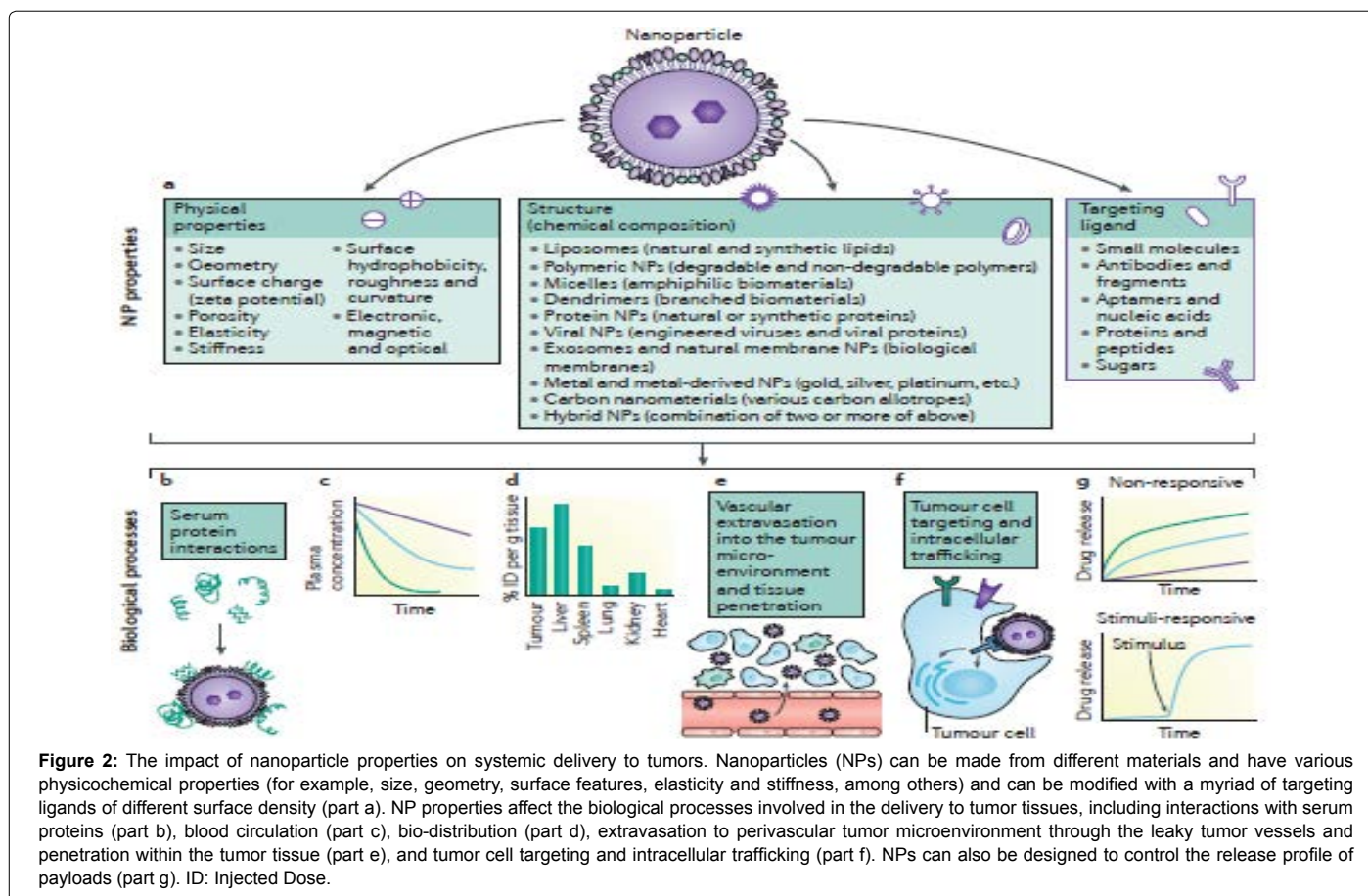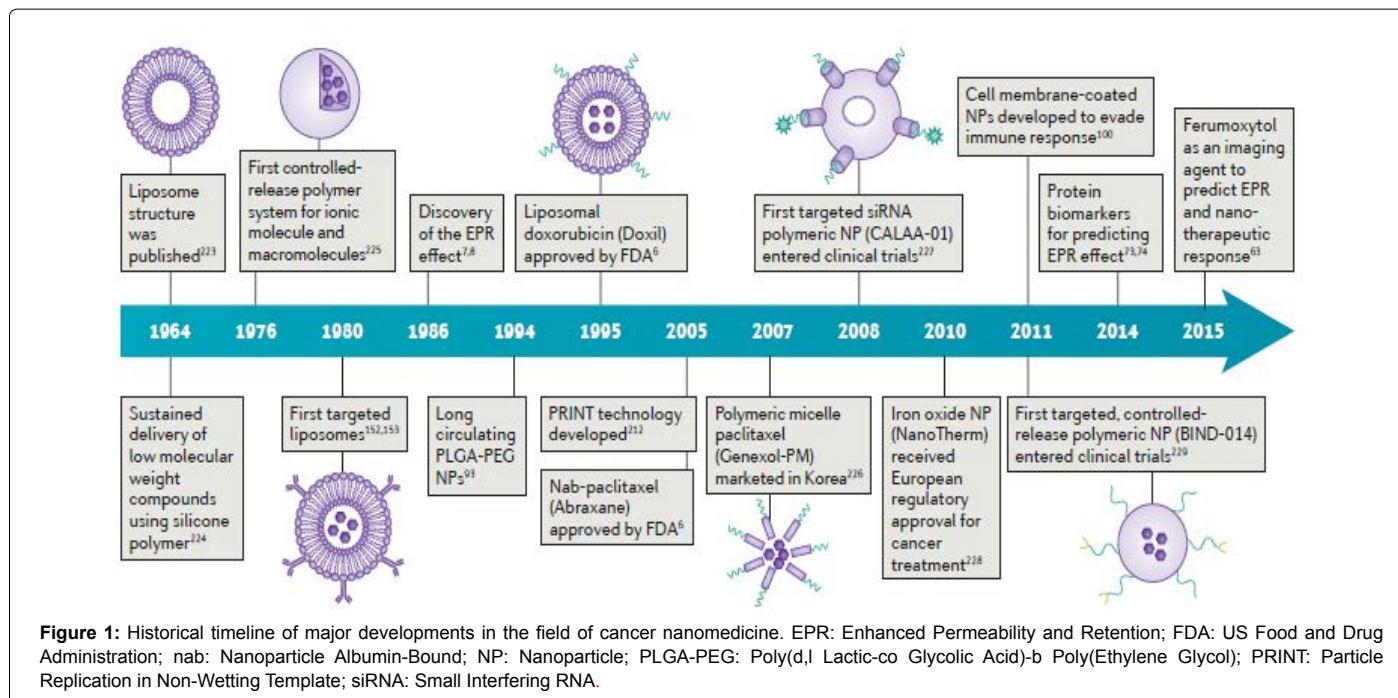
Most therapeutic NPs for solid tumour treatment are administered systemically; they accumulate in a tumor through the enhanced permeability and retention (EPR) effect [5-8], this is due to the product of poor lymphatic drainage and tumor vasculature. The interpretation of EPR is however oversimplified since multiple biological steps in the systemic delivery of NPs can influence the effect NP-protein interactions, blood circulation, and tumor cell internalization. NP properties like size, geometry, surface composition and porosity can influence the biological processes and this determines the EPR effects and the therapeutic incomes (Figure 2). However, most of the current understanding of NP is based on *in vivo* animal data and its translation in humans remains largely a challenge. Pharmacokinetics (PK) of nanotherapeutics across species in preclinical and clinical studies have been explored but so far, only a few have correlated data across species to determine whether and how NP safety and efficacy in humans can be better predicted from preclinical animal models [6].

Figure 1: Historical timeline of major developments in the field of cancer nanomedicine. EPR: Enhanced Permeability and Retention; FDA: US Food and Drug Administration; nab: Nanoparticle Albumin-Bound; NP: Nanoparticle; PLGA-PEG: Poly(d,l Lactic-co Glycolic Acid)-b Poly(Ethylene Glycol); PRINT: Particle Replication in Non-Wetting Template; siRNA: Small Interfering RNA.

Figure 2: The impact of nanoparticle properties on systemic delivery to tumors. Nanoparticles (NPs) can be made from different materials and have various physicochemical properties (for example, size, geometry, surface features, elasticity and stiffness, among others) and can be modified with a myriad of targeting ligands of different surface density (part a). NP properties affect the biological processes involved in the delivery to tumor tissues, including interactions with serum proteins (part b), blood circulation (part c), bio-distribution (part d), extravasation to perivascular tumor microenvironment through the leaky tumor vessels and penetration within the tumor tissue (part e), and tumor cell targeting and intracellular trafficking (part f). NPs can also be designed to control the release profile of payloads (part g). ID: Injected Dose.

Nanotechnology Principles in the Treatment of Cancer

Drugs used in conventional chemotherapy kill cancer cells effectively. There are many unintended side effects due to the cytotoxicity which destroys healthy cells in addition to tumor cells. Chemotherapeutics uses NPs as drug carriers which deliver medication directly to tumors and spare the healthy tissues. These nanocarriers

have many advantages in comparison to conventional chemotherapy [7]. Nanomaterials offer several advantages as drug carriers but evidently the drug particles that are large have a difficulty in reaching the remote and secluded areas of the body [4]. The particles should be small enough with nanoscale dimensions to penetrate across the cell boundary due to the small size of thecell. The tiny capillaries have 5-6 micron diameter, and most of the microparticles cannot pass through them. So NPs are more suitable than microparticles for intravenous delivery [8]. For systemic circulation, the particle diameters should lie in the range of 10-100 nm to have access to various parts of the body. Nanomaterials are consumed by cells efficiently than comparatively larger micromolecules and this raises the drug effectiveness. The NPs have the drugs attached to their surface or it is integrated into the matrix.

The dissolution rate is also increased since NPs possess very high surface to volume ratio. For example, when formulated as nanosuspensions, poorly soluble drugs like paclitaxel, cyclosporine, or amphotericin B exhibit an increased rate of dissolution and absorption in the gastrointestinal tract [9]. Thirdly, nanomaterials improve the uptake of a poorly soluble drug through targeted drug delivery at the particular disease site [10]. Depending on the particle charge, surface properties, and relative hydrophobicity, NPs are formulated to adsorb preferentially on organs or tissues. Lastly, nanomaterials help in the lessening of undesirable side effects by a controlled release. Protection against degradation and to ensure prolonged exposures of the drugs by restricted release, the drugs are nanosphere encapsulated and this is a preferred quality of any chemotherapeutic agent [8]. The use of nanomaterials in pharmaceutical sector has provided the solutions for delivery problems and improved therapeutic index. Nanomaterial-based drug carriers can protect drugs from being degraded in the body before they reach their target, and increase bioavailability to obtain the best effect from it [11]. It has also reduced the chances of the drugs interacting with normal cells hence avoiding adverse side effects while enhancing the absorption into tumors and the cancerous cells.

Passive Tumor Targeting

Certain NPs can escape through blood vessel walls and into tissues due to their size and surface properties. Tumors have leaky blood vessel walls and defective lymphatic drainage, these properties enable NPs to accumulate in them [12]. The ability to concentrate the cytotoxic drugs where needed, protection of the healthy tissues from adverse side effects is possible because of these tumor features. Examples of such diseases where passive targeting of can be achieved are the tumor tissues and inflamed tissues. There are several nanocarrier-based drugs in the market, which rely on passive targeting through a process known as enhanced permeability and retention [13].

Active Tumor Targeting

This is based on selective targeting by NPs as a result of the molecules expressed by the cancerous cells. Attaching a molecule to NPs enables targeting of the molecule to a cell that expresses a particular receptor. Active targeting principle is used to deliver drugs into the cancerous cell, by inducing the cell to absorb the nanocarrier [9]. To further reduce the interaction of the carried drugs and healthy tissues active targeting can be combined with passive targeting. The efficacy of a therapeutic can also be increased by nanotechnology-enabled targeting, and this helps to achieve a greater tumor reduction with lower doses of the drug (Table 1) [14].

Passive tumor targeting using NP carriers is a size-depended process. Passive tumor targeting actually occurs due to the pathophysiological characteristics of the tumor vessels - leaky vasculature and poor lymphatic drainage.

Extravasation of particulate materials into the tumor tissue occurs sometimes and these particulate materials can be retained which is termed the enhanced permeation and retention (EPR) effect. However, these particulate materials, recognized as foreign bodies, may be opsonized by the cells of the reticuloendothelial system (mononuclear phagocyte system, MPS), thereby decreasing the availability of the delivered drug at the target site. Well-designed nanocarriers such as those coated with polyethylene glycol (PEGylation), have the ability to escape capture by the MPS. Such drug delivery systems are referred to as the stealth systems [15-36]. Most passive-targeting nanosystems have a surface coated with PEG for biocompatibility and "stealth" purposes. A variety of PEGs having varying chain lengths and molecular weights had been utilized for controlling the thickness of the PEG coating and

S/N	Cancer type	Active ingredients	References
1.	Breast cancer	Doxorubicin, Disulfiram Paclitaxel, siRNAs, Doxorubicin, TRAIL, DNA and Indole-3-carbinol (I3C)	[14-17]
2.	Cervical cancer	Doxorubicin, Vorinostat and siRNA	[18]
3.	Colon cancer	Camptothecin and DNA	[19]
4.	Epidermoid cancer cells (human), MCF-7 breast cancer cells and HCT-116 colon cancer cells	Andrographolide	[20]
5.	Head and neck cancer	Cisplatin and pyrolipid	[21]
6.	Hepatocellular carcinoma	Docetaxel and DNA	[22]
7.	Liver cancer	Doxorubicin and DNA	[23]
8.	Lymphocytic leukemia cells (P388)	Andrographolide	[20]
9.	Melanoma	Oligonucleotide G3139 and d-(KLAKKLAK)$_2$ peptide	[24]
10.	Non-Small cell lung cancer (NSCLC)	Small interference (siRNAs), Doxorubicin and Paclitaxel	[25,26]
11.	Ovarian cancer	Diindolylmethane (DIM)/Indole-3-carbinol (I3C)	[27,28]
12.	Ovarian intraperitoneal metastasis	Paclitaxel and yittrium-90	[29]
13.	Prostate and breast cancer	Cisplatin and siRNAs	[30]
14.	Prostate cancer	siRNA, Doxorubicin, CpG and Oligonucleoyide	[31]
15.	Small cell lung cancer (SCLC)	Irinotecan and cisplatin	[32]
16.	Testicular and small cell lung cancer	Podophyllotoxin and several other compounds (known as lignans)	[33]
17.	Triple-negative breast cancer	Antisense oligonucleotides, Doxorubicin and siRNA	[34,35]

Table 1: *In vivo* examples of NP-mediated combination therapies for cancer treatment in tumor cells.

the grafting efficiency [37]. Longer chains offer greater steric hinderance around the nanocarrier than short chain pegs. Surface modification of nanocarriers can also be achieved by using derivatives of PEG such as the block copolymers of the poloxamer type.

Improving Drug Delivery to the Tumor

NP-protein interactions

The body of NP is rapidly covered various biomolecules when it enters a biological environment like blood or extracellular matrix and this leads to the formation of a corona (Figure 2b). The NP receives a biological identity that determines the physiological responses they elicit, ranging from cellular uptake and intracellular trafficking to PK, bio-distribution and toxicity (Figure 2c-2f). For instance, the binding of opsonins can trigger recognition and clearance by the mononuclear phagocyte system (MPS) [38]. A corona rich in dysopsonin proteins like apolipoproteins and albumin which inhibit phagocytic uptake could contribute to the stealth effect of NPs. the decoration of NPs with some plasma proteins can improve delivery to specific organs while ligand functionalized NPs might lose targeting capability when corona forms on their surface [32,39,40]. One recent example is the finding that apolipoprotein E is essential for some siRNA alipoplexes to target hepatocytes *in vivo*. In contrast, NP-protein interactions in clinical settings can also trigger hypersensitivity reactions in patients by activating the complement system [32].

Blood circulation

The efficiency with which a NP passively extravagates from the microvasculature into the tissue has a relative with blood circulation half-life (Figure 2c). A short blood circulation half-life may be sufficient for desired accumulation in the tumor for tissues with relatively large blood flow and particles that efficiently extravasate from the microcirculation. For poorly perfused tissues or particles that have low extravasation efficiency, a longer circulation half-life is necessary to enhance exposure.

Extravasation to the TME

Extravasation of NPs from the systemic circulation to tumors (Figure 2d and 2e) can be influenced by aberrant tumor vasculature, the perivascular TME and the NP itself. The metabolic demands of rapidly dividing cancer cells result in the formation of neovasculature that is architecturally abnormal and exhibits a 'leakiness' distinct from that occurring with inflammation [40]. Unlike the endothelial lining of a vasculature, which has a turnover of approximately 1,000 days, the endothelium in tumors can double approximately every 10 days and the resulting microvasculature does not have clearly defined morphology with distinct venules, arterioles or capillaries [18].

Tumor penetration

Much emphasis has been put on extravasation and accumulation in NP delivery, but deep and uniform tumor penetration of nanotherapeutics may be crucial for optimal outcomes. For example, studies of macromolecules and antibodies demonstrate that size and binding affinity affect both diffusion kinetics and depth of tissue penetration [22]. Secondly, higher-affinity antibodies that bind to target antigens on cancer cells penetrate tissue less efficiently than lower-affinity antibodies against the same target [26].

Cellular uptake and intracellular trafficking

Nanoparticle retention may be a result of effective cell internalization

since many nanomedicines act on intracellular targets. This has mainly been seen in biomacromolecules that are involved in RNAi pathway like siRNA and microRNA both of which require cytosolic delivery for bioactivity [24]. Targeting ligands that recognize specific receptors on the tumor cell surface are one way by which to improve cellular uptake (Figure 2f). In addition, active targeting is of importance more so when tissue accumulation does not depend on EPR [25]. This has been seen in vascular targeting and in the delivery of therapeutic agents which requires active transcytosis of physiological barriers.

Targeting the TME and the premetastatic niche

Since TME has an importance in tumor development, progression and metastasis and drug resistance, it is also considered a target for cancer treatment. TME offers an alternative strategy for tumor accumulation and penetration of NP strategy [14]. The advantage of targeting non-tumor cells in comparison to tumor cells in TME is their genetic stability and lack of drug resistance development strategy. Besides TME of the primary tumor, the environmental conditions required for metastatic cells to survive and proliferate have also received considerable attention in the development of new therapeutic avenues [15].

Tumor vasculature

A lot of effort has been channeled towards NP-mediated selective drug delivery to the tumor vasculature (Figure 3a) and this is crucial to tumor growth and metastasis. This has been achieved by coating of NPs with ligands that bind specifically to over-expressed receptors such as $\alpha v\beta 3$ integrin [19], on the surface of tumor endothelial cells. *In vivo* studies in mice revealed that inhibiting angiogenesis can cause regression of established tumors or suppression of metastasis. Besides targeted NPs, several non-targeted cationic lipid or polymeric NP platforms have been designed for preferential delivery of siRNA to vascular endothelium [16]. A recent unique formulation called 7C1 specifically reduced the expression of target endothelial genes at low siRNA doses without substantially reducing their expression in pulmonary immune cells, hepatocytes or peritoneal immune cells [31].

Stromal cells

Targeting stromal cells such as tumor-associated fibroblasts and macrophages have also been proposed for cancer treatment (Figure 3a). A unique docetaxel-conjugated NP platform called Cellax significantly depleted α smooth muscle actin (α-SMA)-expressing fibroblasts, reducing tumor ECM and IFP, increasing vascular permeability and suppressing metastasis [33]. This effect is presumably through the adsorption of serum albumin on Cellax, followed by specific interaction with α SMA+ fibroblasts that also express elevated levels of the albumin-binding protein, secreted acidic cysteine-rich glycoprotein (SPARC) [30]. Differentiation of TAMs to a pro-tumorigenic or immunosuppressive (M2 like) phenotype has commonly been associated with tumor progression and poor patient outcome. By inhibiting the activity of signal transducer and activator of transcription 3 (STAT3), hydrazinocurcumin-loaded NPs can 're-educate' TAMs to transform from an M2 like into an antitumorigenic M1 phenotype for inhibited tumor growth. PEG-sheddable, mannose-modified NPs have also been developed to efficiently target TAMs that have elevated expression of mannose receptors, while minimizing uptake by macrophages of the MPS [35].

Metastatic microenvironment

NP delivery to the major sites of metastasis (for example, lungs,
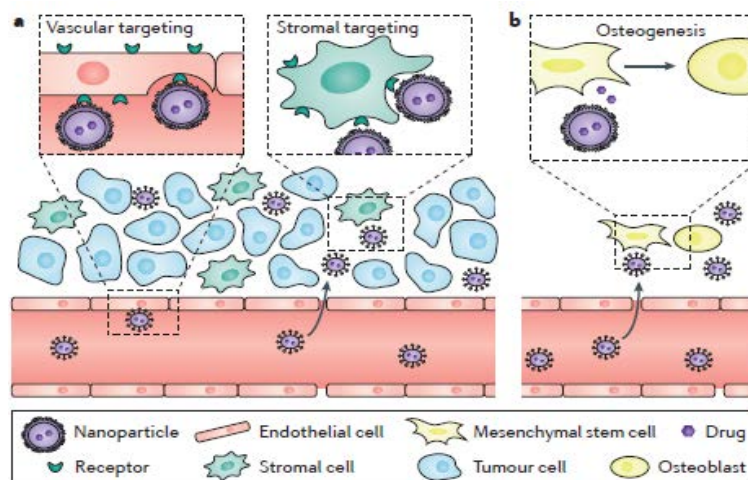
Figure 3: Nanoparticle targeting of the tumor microenvironment and the premetastatic niche. Targeting of the tumor vasculature or stromal cells in the tumor microenvironment (part a) and the premetastatic microenvironments such as the bone marrow niche, where induction of the osteogenic differentiation of mesenchymal stem cells enhances bone strength and volume (part b). Cell-specific targeting can be achieved via the modification of nanoparticles (NPs) with ligands that bind to specific receptors on the surface of tumor endothelial cells, stromal cells or other target cells.

liver, lymph nodes, brain and bone) and metastatic tumor cells themselves have been comprehensively discussed elsewhere. A newly developed system of polymeric micelles formulated from polymer–drug conjugates has shown promising therapeutic efficacy in a mouse model of colon cancer with lung metastasis [17], and in a pilot study of one patient with castration-resistant prostate cancer with lung and bone metastases. Comparatively little effort has been devoted to exploiting nanotechnology to modify the premetastatic microenvironmental niche and suppress tumor growth. In a recent study, a bone-homing polymeric NP platform was engineered for spatiotemporally controlled delivery of therapeutic agents (Figure 3b) [21]. After pretreatment with alendronate-conjugated, bortezomib-loaded polymeric NPs, mice showed significantly slower myeloma tumor growth and prolonged survival. The application of such pretreatment strategies for protecting the organs vulnerable to metastasis could be accelerated by revealing which microenvironmental factors control the intravasation, adhesion and growth.

Nanomedicine for the Future

The major company involved in nanomedicines research for cancer treatment is CytImmune. It was founded in 1988 and has transitioned from a successful diagnostics company into a clinical stage nanomedicine company. Its core focus is on the discovery, development and commercialization of multifunctional tumor targeted therapies.

CytImmune's successful completion of a phase I clinical trial of CYT-6091 has given the company a fore front leadership on the future of nanomedicine. CYT-6091 uses gold NPs to deliver drugs directly to cancer tumors and it uses a combination of techniques to target the NPs to cancer. First, the NPs are designed to be too big to exit most healthy blood vessels. The blood vessels located around tumors are leaky and this allows the NPs to leave the blood vessels to the tumor site. Secondly, molecules of tumor necrosis like factor alpha (TNF-alpha) a tumor killing agent to the NPs as well as molecules of thiol-derivatized polyethylene glycol (PEG-THIOL).

PEG-THIOL helps hide the TNF-alpha bearing the NPs from immune system allowing the NPs in the region of cancer tumor TNF molecule to bind to the cancer cells. CytImmune's patented technology is based on colloidal gold particles that carry specific drugs to the targets like cancer cells [29]. Chitosan NPs can also be effective materials for targeted drug delivery [41]. These particles allow drugs to be safely transported through the bloodstream and direct to a specific target. There are also a few more targeted chemotherapy treatment and nanomedicines under development.

Conclusion

Most of the versatility required to overcome some of the numerous challenging hindrances in the treatment success while using conventional chemotherapeutic agents will soon be history due to the development of cancer nanomedicine. Research should focus on identifying the appropriate NPs that work well with certain chemotherapeutic agents for the drug's cytotoxic effect or the cytotoxic effect of the NPs itself after activating with a suitable form of electromagnetic energy. Studies also should be encouraged to identify and formulate NP-based tests for early identification of cancer. Cancer studies need to hasten the clinical trials, and FDA approval to enable clinicians to use these tests in the clinics conveniently as a preventive measure. In summary, we are rapidly acquiring a much deeper understanding of the challenges and opportunities presented by cancer nanomedicine.

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