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Tumor vasculature vs tumor cell targeting: Understanding the latest trends in using functional nanoparticles for cancer treatment

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ABSTRACT

Delivering drugs to tumors using nanoparticles (NPs) has shown promising potential in promoting targeted drug delivery of antineoplastic agents to enhance their efficiency while reducing the associated systemic toxicity. This review highlights the different types of NPs and the physiological characteristics of the tumor microenvironment (TME), and the mechanisms undertaken to safely deliver drugs to specific lesions. We review the principles and latest developments in the field of targeted NPs designed to target tumor vasculature compared to those designed to target cancer cells and their correlation with the TME. We discuss the advantages and limitations of each targeted drug delivery mechanism and future directions aiming to maximize their potential.

1. Introduction

According to the American Cancer Society, in 2022, around 1.9 million new cases of cancer were diagnosed; in addition, about 609,360 deaths were caused by cancer in the U.S. alone [1]. Normally, cells follow an orderly path of growth, division, and apoptosis. However, cancer cells experience extensive changes on the cellular, genetic, and epigenetic levels, disrupting the natural cell life cycle, leading to uncontrollable cell division and growth, i.e., tumors. If the formed mass is localized, it is referred to as a benign tumor; however, if it invades nearby tissues or spreads to other parts of the body (i.e., metastasizes), the tumor is considered to be malignant [2]. Various environmental, as well as, genetic factors can play a role in cancer occurrence and development. Cancer can be initiated by exposure to carcinogenic substances such as Asbestos and cadmium [3]. Other environmental and lifestyle factors that can also play a role in cancer occurrence include smoking, obesity, alcohol, ultraviolet light, and exposure to ionizing radiation [4]. Genetic instability may cause nucleotide dysfunction, leading to DNA breakage and chromosome translocation; if such injuries are not corrected, it may result in cell mutation and the subsequent uncontrolled growth [5].

Cancer treatment has made considerable progress over the years but remains challenging due to the complexity of achieving precise elimination of tumors and the high chance of reoccurrence. Chemotherapy is widely used to treat a wide range of localized and metastatic tumors. Generally, commercially available antineoplastic agents are designed to destroy cancer cells by arresting their growth and division [6]. They primarily target fast-growing cells, not just cancer cells, including healthy cells such as blood-forming cells, hair follicles, cells in the digestive tract and reproductive system. This indiscriminate attack leads to debilitating side effects

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such as nausea, fatigue, diarrhea, hair loss, infections, mucositis, loss of appetite, and reduced fertility, as well as increasing the risk of heart complications [7]. To overcome these side effects, as well as decrease the chances of cancer reoccurrence and multidrug resistance (MDR), these toxic drugs can be loaded inside small carriers, the main component of smart drug delivery systems (SDDSs). SDDSs are highly efficient in loading one or more of the toxic drugs and safely delivering them to the targeted solid tumor, avoiding their contact with healthy cells. SDDSs are designed to be in the nano-size range (10-100 nm) known as NPs. NPs are diverse drug carriers prepared using different matrix materials and have varying mechanical and physicochemical properties allowing their utilization to treat different types of tumors [8]. Loading highly toxic antineoplastic agents inside NPs enhances drug pharmacokinetics and bioavailability as well as reduces drug resistance [9,10]. Moreover, NPs allow the delivery of poorly soluble drugs, nucleic acids, and other therapeutic agents to tumors [11–16].

Their small size, highly controlled physical and chemical properties, as well as their biocompatibility, make them ideal drug delivery modalities. NPs can be highly selective for certain tumors by conjugating different biological moieties to their surface, thus producing functionalized NPs able to bind to specific receptors overexpressed on the surfaces of targeted tumors. Once at the targeted site, NPs can be designed to allow the sustained release of the loaded drugs. Furthermore, the loaded NPs can be designed to be sensitive to certain triggers which can initiate and control drug release. This will ensure the delivery of the required dose of drugs at a precise time with high specificity to tumor tissues. This results in the accumulation of high concentrations of the toxic drugs inside the cancerous tissues while sparing the healthy tissues, which will reflect positively on patients' response to treatment regimens as well as their quality of life [17,18].

Employing NPs to successfully deliver drugs to tumors depends on understanding tumors and their growth mechanisms. Cancer cells invade host tissues and stimulate many cellular, molecular, and physical changes to reinforce and support their fast growth and continuous progression. This results in creating a unique TME. TME is a complex structure that continues to evolve as tumors grow. The composition of TME varies depending on tumors' type and stage. Generally, TME includes cancer cells, immune cells (such as natural killer cells, lymphocytes, and macrophages), stromal cells (such as fibroblasts and pericytes), vascular tissues, and extracellular matrix (ECM) [19]. TME promotes cancer progression; the mutual and dynamic relationship between cancer cells and the different elements of the TME aims to support tumor survival, growth, and metastasis [20]. The extensive research to understand TME continues to identify potential targets for NPs within the different TME components to facilitate the delivery of the required therapeutic doses to suppress tumor growth while reducing the unwanted side effects. Targeting cancer cells, as well as tumor vasculature, using NPs has attracted great interest compared to other components of TME. Furthermore, the unique characteristics of TME can be utilized to trigger drug release from loaded NPs (internal triggers) to secure successful and efficient drug release once inside tumors. In this review, we discuss the concepts and mechanisms of both tumor targeting strategies summarizing representative examples and the latest developments of each approach, highlighting their benefits and limitations, as well as the future directions leading to designing a more advanced NPs for a highly efficient drug delivery to treat solid tumors.

2. Tumor vasculature and angiogenesis

Normal blood vasculature is designed to provide the needed blood supply carrying oxygen and nutrients to all cells making up the body's different tissues. However, as solid tumors grow in size, their demand for oxygen and nutrients increases to a level beyond the supply provided by normal vasculature. To overcome this limitation, boosting the formation of new and fresh blood vessels is essential. Tumor vasculatures are able to continuously develop new blood vessels to cover the needs of the fast-growing mass, which is crucial for tumors to grow and thrive. The formation of new blood vessels can be induced through various mechanisms [21]. However, although the developed tumor vasculature aims to support blood supply to cancer cells, the new rapidly formed blood vessels are chaotic, immature, and excessively branched with varying diameters and shunts, leading to the abnormal organization, function, and structure of these vessels [22]. This causes heterogeneous and comprised blood flow [23,24]. The abnormal structure of tumor vasculature creates and maintains a unique TME with specific features limited to tumors. Generally, TME is acidic (lower pH due to the anaerobic metabolism of cancer cells), hypoxic (less oxygenated due to the comprised blood flow), and immunosuppressive (able to attract/develop immunosuppressive immune cells and reduce the efficiency of T-cells). The tough conditions of TME limit the delivery and efficiency of chemotherapeutic drugs as well as other cancer treatments such as radiotherapy and immunotherapy [25].

Tumor vascularization can be induced through various mechanisms such as angiogenesis, vasculogenesis, vessel co-option, and vascular mimicry (also known as vessel mimicry) [21,26,27]. Angiogenesis is defined as the formation of new blood vessels from the proliferation of endothelial cells of an existing blood vessel [28]. The process occurs in normal tissues of growing organisms, wound healing, and tumors. It is often associated with tumor progression and metastasis; however, it is important to mention that tumor metastasis can also be induced without angiogenesis. For example, vessel co-option is a non-angiogenic route of blood supply for tumors to metastasize. It is often reported in highly vascularized tissues such as the liver, lungs, and brain [26]. Angiogenesis is widely studied as the primary mechanism for blood supply to tumors. The mechanism is regulated by creating a balance between pro- and anti-angiogenic factors. When these factors are balanced, the vasculature system is quiescent [28]. However, when the pro-angiogenic factors become dominant (known as the "angiogenic switch"), endothelial cells start to proliferate to form new blood vessels [28]. The onset of the angiogenic switch may occur at any point during tumor progression, depending on the type of the tumor and its TME [29].

Generally, angiogenesis takes place in blood capillaries which are the smallest blood vessels with a few micrometers in diameter (~8 μm) and one micrometer in thickness [30]. Their function is to exchange oxygen, nutrients and metabolites between blood and tissues. Blood capillaries are made of a single and uniformed endothelial layer surrounded by a homogenous basement membrane and supported by mature pericytes [28]. This allows for normal blood flow and sufficient delivery of oxygen to the surrounding tissues to

carry out aerobic respiration. However, as tumors' size increases, their demand for oxygen and nutrients also increases. This leads to triggering pathological angiogenesis to increase blood supply to the growing tumor mass. The uncontrolled growth rate results in producing endothelial cells with irregular shapes; they are usually unorganized, stacked, and do not form a normal monolayer. Furthermore, the intermittent basement membrane of the newly formed blood vessels and the immature Pericyte detachment make them highly unstable with high vascular permeability (leaky walls) (Fig. 1). These abnormalities lead to an unstable and heterogeneous blood flow as well as increased interstitial fluid pressure (IFP) as fluids continue to extravasate through the leaky vessels. While the approximate IFP of normal tissues is 0 mmHg, the IFP of tumor tissues can be as high as 10-40 mmHg [31]. High levels of IFP add more pressure on the already deformed vessels and contribute to the development of a non-functional lymphatic drainage system [32]. This creates a phenomenon known as the enhanced permeability and retention (EPR) effect. The irregular structure of tumor vessels allows cancer cells to escape through the leaky vessels to other parts of the body, promoting metastasis. Furthermore, the abnormal tumor vasculature creates a unique hypoxic and acidic TME, which promotes tumor development, metastasis, and resistance to chemotherapeutic drugs [33]. Both hypoxia and acidosis of TME play an essential role in attracting and developing immunosuppressive immune cells, reducing T cells as well as reducing the efficiency of cancer treatment.

There are two types of angiogenesis: sprouting angiogenesis and intussusceptive angiogenesis. Of both types, sprouting angiogenesis is better understood due to its early discovery (nearly 200 years ago) compared to intussusceptive angiogenesis, which was discovered two decades ago. Both types of tumor angiogenesis can be triggered by hypoxia and occur in all tissues and organs. However, while sprouting angiogenesis forms new capillary vessels out of pre-existing ones by creating sprouts of endothelial cells, intussusceptive angiogenesis, also known as splitting angiogenesis, occurs by splitting existing blood vessels into two [34].

2.1. Sprouting angiogenesis

When a tumor grows a few millimeters in diameter, it increases the demand for oxygen and nutrients. As a result, hypoxic conditions trigger the "angiogenic switch" by releasing a cocktail of pro-angiogenic factors to TME [35]. Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2), apelin (APLN), ephrins, angiopoietins (ANGPTs), and chemokines are the main pro-angiogenic factors orchestrating angiogenesis [28]. The interaction between nearby cells and growth factors releases them from a quiescent to an active state and sparks a series of events that eventually become uncontrolled. Sprouting angiogenesis (SA) is induced by the angiogenic switch; the process is summarized in three steps: tip cell selection, sprout extension, and, finally, lumen formation [28]. Fig. 2 illustrates the steps involved in sprouting angiogenesis.

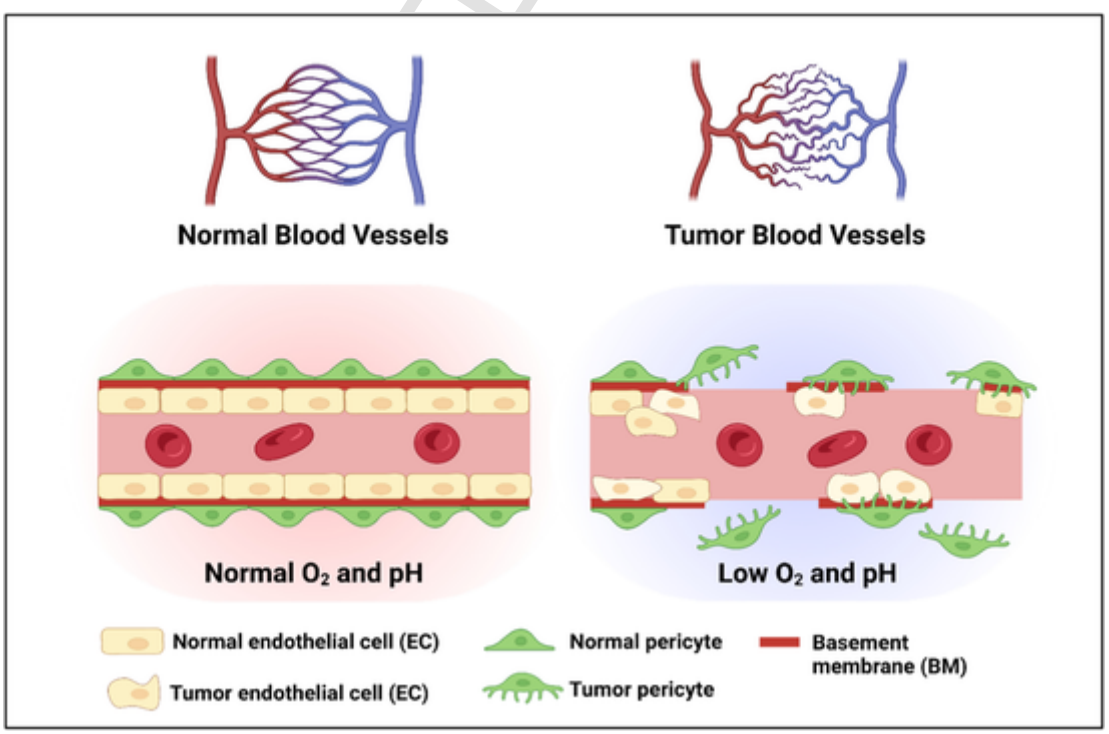


Fig. 1. Normal well-organized blood vasculature compared to the chaotic and abnormal organization of tumor vasculature. Healthy vessels have homogenous basement membrane (BM), adherent monolayer of ECs and mature Pericytes coverage compared to the abnormal structure and function of tumor vasculature with heterogeneous BM, irregularly stacked ECs (which obstruct blood flow) and vessel immature Pericyte detachment. The irregular structure of tumor vasculature allows cancer cells to escape through the leaky vessels promoting tumor metastasis. Furthermore, the abnormal tumor vasculature creates a unique hypoxic and acidic TME characterized by high IFP and elevated temperatures.

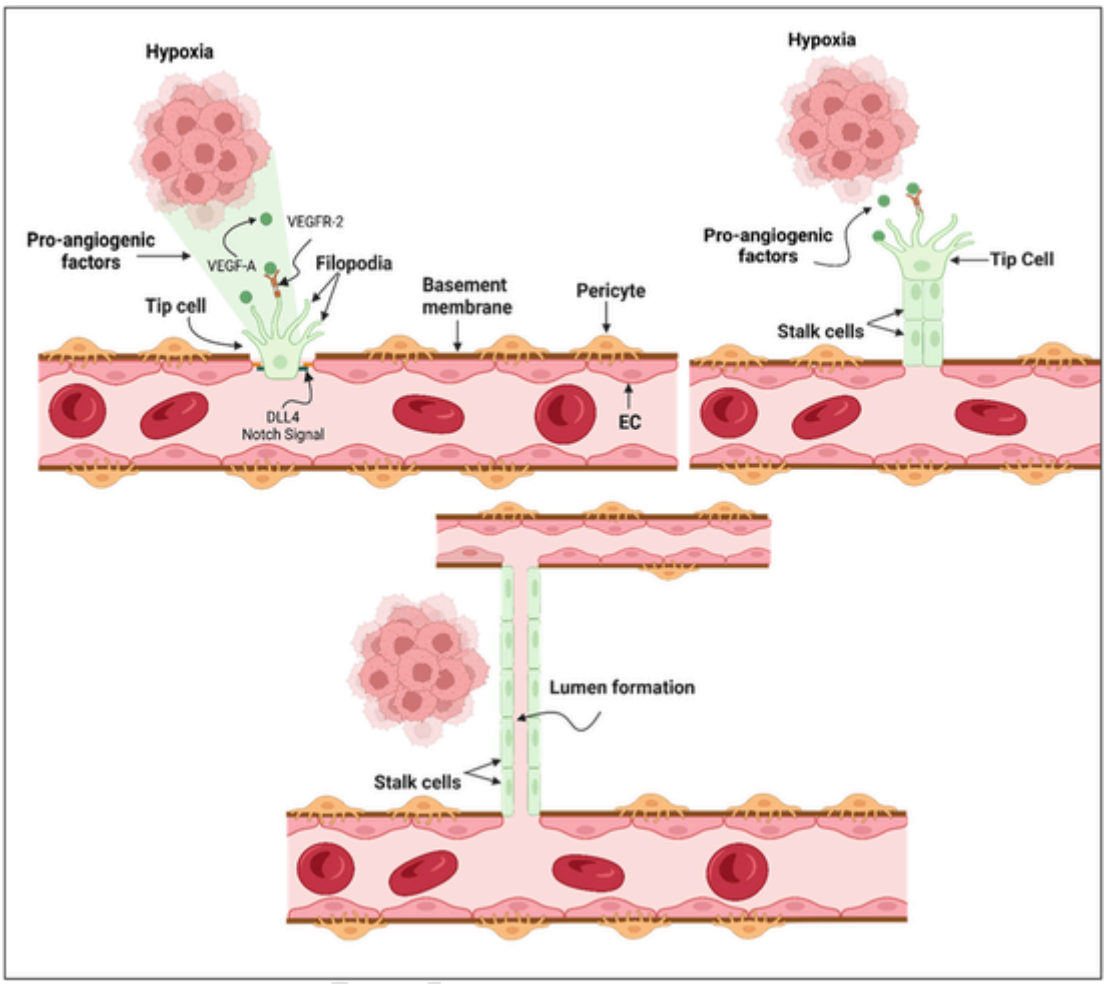


Fig. 2. Sprouting angiogenesis. (A) Tip cell selection, filopodia and notch signaling, (B) Sprout extension by stalk cells proliferation, (C) Lumen formation and the fusion of two sprouts (anastomosis). Created with BioRender.com.

Sprouting angiogenesis starts when tumor cells release growth factors such as the vascular endothelial growth factor (VEGF), which induce sprouting in capillaries. VEGF-A, simply referred to by VEGF, binds to the corresponding tyrosine kinase receptors: VEGFR-1, VEGFR-2, and VEGFR-3, also known as Flt-1, KDR/Flk-1, and Flt-4, respectively [36]. In the vicinity of a tumor, one cell in a nearby capillary becomes the leading cell (known as the tip cell) upon receiving the highest dose of VEGF that binds to VEGFR-2. The neighboring cells become stalk cells which are blocked from converting to tip cells via Notch signaling. VEGFR-2 signaling induces the formation of VEGFR-3 in tip cells, while Notch signaling downregulates the expression of VEGFR-2 and VEGFR-3 in stalk cells. Blocking VEGFR-3 in stalk cells disables them from developing sprouts and protrusions [37]. Notch signaling is activated laterally through Delta-like-4 (DLL4) ligand, which induces VEGFR-1 expression and reduces the expression of VEGFR-2, VEGFR-3, neuropilin-1 (NRP1), and CXCR4 [37]. Hence, cells adjacent to the tip cell become stalk cells. DLL4 ligand is produced by the tip cell in response to VEGF. In addition, other receptors are also expressed on the tip cell, such as VEGFR-2, VEGFR-3, NRP1, platelet-derived growth factor beta polypeptide (PDGF-B), and others [28,37]. In general, tip cells express various types of proteins: proteins needed in the breakdown of the extracellular matrix, proteins involved in the formation of the basement membrane, and proteins that regulate the proliferation of stalk cells [38,39].

Unlike stalk cells, tip cells are non-proliferative migratory cells that do not form a lumen. Tip cells navigate and sense the surrounding microenvironment by antenna-like structures called filopodia. This allows stalk cells to elongate in the direction of VEGF concentration gradient. In response to VEGF, VEGFR-2 signaling and Rho small GTPase proteins regulate the formation of filopodia [37]. Those are membrane protrusions that contain filamentous actin (F-actin), a linear polymer of globular actin (G-actin) subunits. Polymerization of G-actin by proteins of Profilin, Ena/Vasp, and Formin extends F-actin fibers, which induce cell migration [37]. Upon reaching the extracellular matrix (ECM), filopodia form contact points with ECM constituents such as collagen, fibronectin, and laminin, which are regulated by the focal adhesion kinase process, thus pulling the trailing cells forward [37]. For further details on filopodia formation and regulation, refer to De Smet et al. [37]. After lumen formation, blood flows from the parent vessel into the

newly developed sprout. Then, the sprout fuses with another sprout or an existing blood vessel through a process called "anastomosis".

Finally, stalk cells mature into "phalanx cells," characterized by an ordered monolayer of endothelial cells proliferating at a slower rate than stalk cells [38]. During the maturation of phalanx cells, they develop tight junctions and a basement membrane that binds to pericytes. Stalk cells' proliferation and maturation are controlled by the TIE2-ANGPT1/ANGPT2 signaling pathway. Stalk cells express TIE2 and APJ receptors [38]. The binding of ANGPT1 to the TIE2 receptor activates the latter, slows proliferation, and induces vascular maturation. On the other hand, TIE2-ANGPT2 interaction deactivates the receptor, thus, enabling stalk cells to proliferate. Table 1 shows the main pro-angiogenic factors and their role in angiogenesis.

2.2. Intussusceptive angiogenesis

Intussusceptive angiogenesis (IA), also known as "splitting angiogenesis," was identified in 1986 by Caduff and co-workers when they observed small holes in the developing lung vasculature. The mechanisms leading to IA are not fully understood [51]. However, like sprouting angiogenesis, intussusceptive angiogenesis is believed to be affected by the angiogenic switch and the secretion of VEGF [52]. More importantly, hemodynamic forces resulting from blood flow are believed to play a major role in IA [38,52] IA process is faster than SA, and during the stages of IA, there are fewer chances of leakage from blood vessels because the basement membrane does not disintegrate as opposed to the basement membrane in SA [38]. In addition, endothelial cells in IA experience less proliferation than those in SA; instead, they increase in size and flatten [38,52] In IA, the vasculature is remodeled by transluminal pillars within the vessel in response to growth factors such as VEGF, PDGF, and erythropoietin. As shown in Fig. 3, the process is initiated when protrusions from opposite sides of the endothelial walls meet to form an intraluminal pillar. Then, the interendothelial junctions are reorganized, and a void is formed [38]. Pericytes and myofibroblasts then deposit the extracellular matrix into the pillar. Finally, as the pillar grows, it splits the original capillary into two capillaries, thus termed splitting angiogenesis [38].

3. Nanoparticles and their use for chemotherapeutic delivery applications

Medical nanotechnology has been extensively used in cancer diagnostics and for delivering chemotherapeutic agents safely and effectively. NPs, used as drug carriers, are loaded with therapeutic agents, and injected intravenously to deliver their load to the targeted neoplastic sites. The same type of NP system can be used for diagnostic and therapeutic purposes (theranostic NPs). Theranostic NPs can deliver drugs while providing real-time monitoring of the tumor due to their unique optical properties [53]. NPs have shown several advantages over conventional chemotherapy, such as the temporal and spatial targeting of the diseased site, enhanced drug pharmacokinetics, bioavailability, and decreased drug resistance [9,10]. Moreover, NPs can deliver poorly soluble drugs, nucleic acids, and other therapeutic agents [11,12]. Researchers have developed a wide range of promising NPs prepared using either organic or inorganic materials, giving them diverse physical properties, shapes, and sizes. NPs' size is a very important factor in their bioavailability, NPs that are too small (<5 nm) are rapidly cleared from circulation by the immune system. Furthermore, microparticles that are large in size (>220 nm) were found to accumulate in body organs such as the liver and spleen [54]. Generally, clinically approved

Table 1
The main pro-angiogenic factors and their role in angiogenesis.

Pro-angiogenic factor	Role in angiogenesis	Ref.
VEGF	VEGFR-2 activated by VEGF regulates endothelial cells: Survival and proliferation: ERK and PI3K/Akt pathways Migration: PI3K stimulation and Rho GTPases activation Invasion (ECM and basal membrane degradation): plasminogen activator (PA) and matrix metalloproteinases (MMPs) Permeability of the blood vessel.	[28,40–42]
FGF-2/ bFGF	FGFR activated by FGF-2 via paracrine signaling contributes to: Endothelial cells survival, proliferation, migration, proteinase production and angiogenesis Upregulation of MMPs, plasminogen activator and collagenase production for ECM degradation and remodeling Formation of tight junction expressing VE-cadherin in endothelial cells FGF-VEGF crosstalk. FGF-induced signaling suppresses VEGFR signaling	[28,43,44]
PDGF	Pericyte recruitment to stabilize newly formed vessels	[28,45]
ANGPTs	ANGPT-1 and ANGPT-2 are activated by TIE-1 and TIE-2 receptors: Binding of ANGPT-1 to TIE-2 results in vessel maturation and stabilization Binding of ANGPT-2 to TIE-2 results in pericytes detachment, vessels destabilization and ECM degradation	[28]
Eph/ephrin signaling	High expression of EphA2 receptor and its ligand ephrinA1 is associated with tumor angiogenesis and cancers of breast, lung, prostate, lung, and melanomas EphB4-ephrinB2 signaling showed conflicting responses depending on the cell type and the microenvironment. The interaction of EphB4 expressed by cancer cells and ephrinB2 present on ECs may cause angiogenesis to progress and, in some cases, may suppress EC sprouting and angiogenesis EphrinB2 regulates the internalization of VEGFR2, hence controlling its downstream signaling and tumor angiogenesis EphB4 is a tumor suppressor in breast and colon cancer but not in melanoma, prostate, and bladder metastasis	[28,46–49]
APLN/APLNR signaling	APLN promotes tumor cell proliferation, migration, and metastasis APLN expression is upregulated in tumor angiogenesis The outcomes of APLN/APLNR signaling depend on the tumor type and the microenvironment.	[28,50]

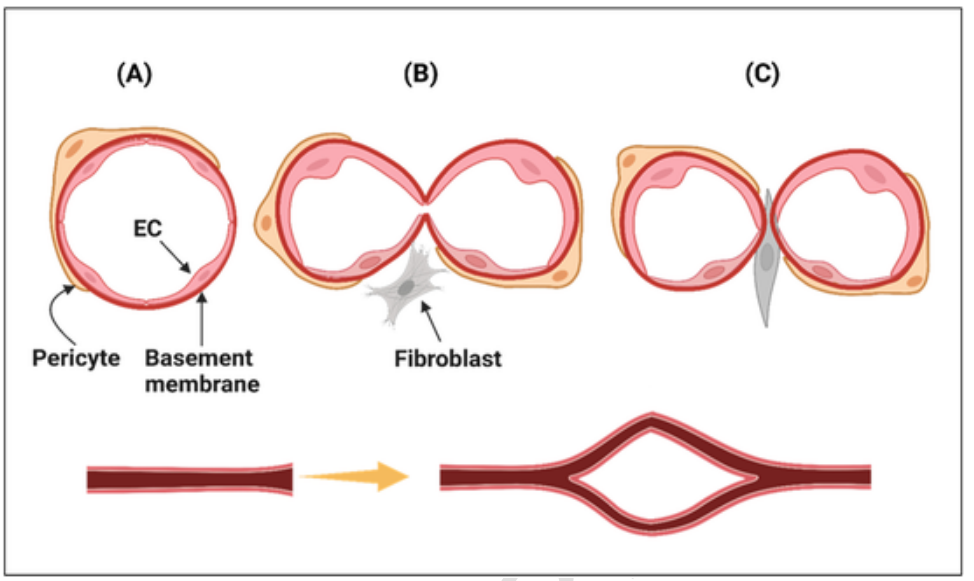


Fig. 3. Sprouting angiogenesis. (A) Cross section of a normal blood capillary, (B) Pillar formation, (C) Vascular splitting. Created with BioRender.com.

NPs range in size between 60 nm and 100 nm [55]. Successful NPs are expected to be safe for use in humans (biocompatible), lacking immunogenicity, with high efficiency in loading drugs and delivering them to targeted tumors [56]. The successful synthesis of efficient NPs can be achieved using physical, chemical, or biological routes. Table 2 shows the different synthesis routes of NPs together with their advantages and disadvantages.

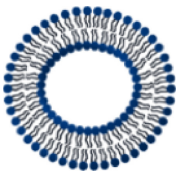
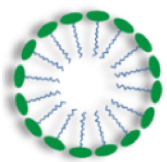
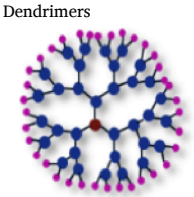
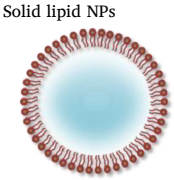
Table 3 and Table 4 summarize the most utilized organic and inorganic NPs listing their most common size range, shape, synthesis methods, advantages, and disadvantages. NPs can be loaded with a wide range of drugs with different action mechanisms aiming to stop the proliferation of cancer cells by hindering their cell division process or by starving the cells by interrupting the flow of oxygen and nutrients needed for supplying their high metabolic demands.

Both physical and chemical synthesis of NPs are widely used in nanomedicine research. However, an emerging and exciting area of nanotechnology involves the use of biological methods to synthesize green NPs. The green synthesis of NPs provides many advantages over the conventional physical and chemical methods, such as increased biocompatibility and reduced environmental hazards. The non-toxic and eco-friendly synthesis technique is simple and effective (Hathout, 2022). The toxic chemicals usually used as reducing agents and stabilizing agents are replaced with green materials such as plant extracts, biological enzymatic reactions, and polysaccharides. Furthermore, green metallic NPs showed higher stability with the desired shape and size compared to other metallic NPs prepared conventionally [63]. A number of recent studies have shown that the green synthesized AgNPs [64], AuNPs [65,66], ZnO [67], and CuO NPs [68] are highly effective and can be efficiently used for the treatment of different types of tumors.

Table 2
The different synthesis routes of NPs, together with their advantages and disadvantages

Synthesis route	Methods used	Advantages	Disadvantages	Ref
Physical	-Evaporation-condensation -Laser ablation, -Thermal decomposition -Ultrasonic spray pyrolysis	-No hazardous solvents -High control of the size and morphology of NPs	-Expensive equipment -High energy consumption -Long times to reach thermal stability	[57, 58]
Chemical	-Microemulsion technique -Sol–gel formation -Hydrothermal synthesis -Flame spraying synthesis	-Self-assembled molecules -Size is controlled by varying the volume of organic solvents/reagents	-Environmental damage - Uses toxic reagents and chemicals -The high cost of reagents	[59, 60]
Biological	-Microorganism-assisted biogenesis -Bio-templates assisted biogenesis -Plant-extract assisted biogenesis	-Non-toxic, eco-friendly -No toxic reagents and chemicals -Highly cost effective	-Difficult to control size and shape of NPs. -Large-scale production of NPs is not feasible.	[61, 62]

Table 3
Summary of the advantages and disadvantages of some organic-based Nanocarriers [74–79].

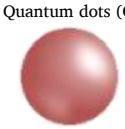
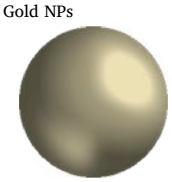
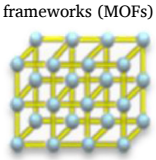
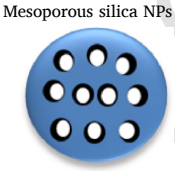
Type	Size Range (nm)	Shape	Synthesis methods	Advantages	Disadvantages
Liposomes 	50nm to several micrometers	Spherical	-Thin film hydration -Reverse phase evaporation -Solvent injection -Detergent removal -Dehydration-rehydration -Heating method -Microfluidic channels -Supercritical fluids method	-Chemical composition mimics that of cell membranes -Biocompatible, non-immunogenic -Reduced toxicity of the encapsulated drug -Improved kinetics and therapeutic index of the drug -High drug loading and small particle size -Facile stealth functionalization -Can load both hydrophilic and hydrophobic drugs -Controllable kinetics of drug release -PEGylation significantly enhances stability and prolongs circulation times	-Possibility of phospholipid oxidation -High production costs -Low solubility -Constrained storage conditions -Lipid bilayer can maximally tolerate about 5%–6% mol% of polyethylene glycol (PEG)
Micelles 	1-100	-Spherical -Reverse micelle -Cylindrical	-Solvent switch -Rehydration -pH tuning in pure water -Polymerization-induced self-assembly (PISA) -Centrifugation-induced self-assembly -Microfluidic channels	-Easy self-assembly synthesis procedures -Small particle size -High drug loading -Water-soluble -Biocompatible -Controllable release rates	-Difficulty of large-scale production -Long processing time -Limited shelf life -Delivery is limited to lipophilic drugs -Structural stability is highly dependent on the critical micellar concentration and temperatures -High occurrences of premature drug release
Dendrimers 	1-10	-3D globular branched shape	-Divergent method -Convergent method	-Tunable chemical and physical properties -Covalently associate the drugs -Solubility enhancing properties -Flexibility in conjugation properties -Effective *in vitro* cytotoxicity due to their surface catatonic groups	-High synthesis costs -Their metabolism depends on the generation and materials -Poor drug release profile -Instability and air sensitivity -Toxic to normal tissues because of interactions with cell membranes -PEGylation significantly lowers their toxicity to tumors but is needed for prolonging their circulation times; thus careful design optimization of these parameters is necessary
Solid lipid NPs 	10 nm-1 μm	-Spherical -Platelet/ disc-like	-Supercritical fluid technique -High-pressure homogenization -Ultrasonication -Microwave-assisted -Microemulsion -Double emulsion -Phase inversion temperature -Membrane contractor -Emulsification-solvent evaporation -Emulsification-solvent diffusion -Solvent injection	-Possible Large-scale production -Low toxicity -Can incorporate both hydrophilic and hydrophobic drugs -Lower production costs compared to liposomes	-Drug expulsion during storage due to polymorphism -Risks of gelation -Low drug-loading capacities

(*continued on next page*)

Table 3 (*continued*)

Type	Size Range (nm)	Shape	Synthesis methods	Advantages	Disadvantages
Niosomes 	25-100	-Spherical	-Thin-film hydration -Solvent injection -Reverse-phase evaporation method, transmembrane pH gradient drug uptake process, bubble method, and micro-fluidization method	-Ability to encapsulate hydrophilic and hydrophobic drugs -Good stability, low cost, easy to be formulated and scaling-up	-Increased polyoxymethylene chain length can induce increased cytotoxicity -Drug leakage due to particles aggregation, hydrolysis, and fusion issues

Table 4
Summary of the advantages and disadvantages of some inorganic-based nanocarriers [74,75,80–84].

Type	Size Range (nm)	Shape	Synthesis methods	Advantages	Disadvantages
Quantum dots (QDs) 	2-10	-Cuboid -Cylindrical -Pyramidal -Conical -Lens shaped	-Molecular beam epitaxy (MBE) - Ion implantation - e-beam lithography - X-ray lithography -Self-assembly in solution following chemical reduction	-Imaging properties: high quality and high energy fluorescence -High photostability -Narrow peak of emission -Versatile surface chemistry -Long shelf-time - Emission is controlled by QDs size and structure	-High *in vivo* toxicity -Instability and increase in hydrodynamic diameter upon interactions with serum proteins -Non-PEGylated formulations experience high non-specific uptake by the RES
Gold NPs 	5-400	-Triangular -Cuboidal -Octahedral -Disc-like	-Laser ablation -Ion sputtering -UV irradiation -IR irradiation -Aerosol technology -Reduction of Au^{3+} to Au^{0}	-Increased contrast -Controlled particle size -Able to convert light into heat used to destroy tumors. -Easy surface functionalization and modification: pegylation significantly enhances their solubility and stability	-Non-biodegradable -High cost for large-scale production -Aggregation and stability issues -Size-dependent cytotoxicity
Carbon nanotubes (CNTs) 	0.4-40	-Single-walled or multi-walled cylindrical	-Chemical vapor deposition (CVD) -Carbon arc -Laser ablation	-Ability to load large drug molecules -Sustained-release profiles -Large surface area -Easy conjugation to multiple bioactive agents -Strong optical absorption in the near-infrared region	-Degradation of cargo by lysosomes -Poor solubility in water and poor pK -Toxicity concerns -Non-biodegradable -Synthesis must be under controlled conditions to achieve homogenous size, shape, mechanical strength and purity distributions
Metal- organic frameworks (MOFs) 	10nm-200μm	-Thin films -Hollow superstructures	-Solvothermal -Slow diffusion -Layer-by-layer deposition -Microwave assisted -Sonochemical -Electrochemical -Mechanochemical	-High surface area and porosity for high loading efficiency -Facile modification of physical (e.g., pore size and shape) and chemical properties of MOFs -Biodegradable -Well-defined structures are beneficial for host–guest interactions -Amphiphilic pore features	-The open metal centers pose cytotoxic limitations and stability issues in humid conditions -Non-biodegradable -Poor drug release profile -Toxicity concerns
Mesoporous silica NPs 	2-50	-Film -Ellipsoid -Rod/hollow rod -Spherical -Cuboidal -Disc	-Sol-gel	-Large surface area -Stable -Controllable porosity -Ease of functionalization and high surface reactivity	-High *in vivo* cytotoxicity -Rigid structure -Polydisperse size distribution -Silica NPs are hepatotoxic -Have been associated with undesirable side effects on the immune system -Size-dependent cytotoxicity

4. Passive and active targeting of tumors using NPs

Both passive and active targeting strategies aim to achieve the successful accumulation of NPs inside tumors by exploiting the unique pathophysiological characteristics of tumors. During passive targeting of tumors, NPs (less than 200 nm) can benefit from the EPR effect, limited to tumors, since their small size allows them to extravasate through the leaky tumor vasculature and accumulate inside tumor tissues due to their impaired lymphatic drainage system [69,70] which aids in the successful delivery of NPs [71]. On

the other hand, forming vascular sprout is a highly complex process that involves precise coordination between the actions of several cancer biomarkers, such as "selective receptors," which are overexpressed on the surfaces of the endothelial cells forming the tumor vascular system. The overexpression of these receptors is found in almost all solid tumors (Fig. 4). The importance of tumor vasculature for tumor survival, growth, and metastasis rendered them an attractive and highly desirable target for therapeutic NPs. NPs can be designed to target specific receptors highly overexpressed on tumor vasculature. These are known as functionalized NPs or targeted NPs. Targeted NPs are conjugated to selected molecules that can bind to targeted receptors to initiate endocytosis. This is known as "active targeting". NPs targeting tumor vasculature have proven to be an important and promising direction in cancer therapy. It allows the delivery of various payloads with high precision to tumors [25,27,69,72]. As well as targeting tumor vasculature, drug-loaded NPs can be designed to target cancer cells by binding to the overexpressed receptors located on the surface of these cells following their extravasation through the leaky tumor vessels allowing highly precise delivery of their loads to the diseased cells [25,27,72,73].

Functionalized NPs targeting tumor vasculature deliver their loads inside the vessels without crossing to the cancerous tissue; they are independent of the EPR effect. On the other hand, like plain NPs designed for the passive targeting of tumors, functionalized NPs targeting cancer cells also depend heavily on the EPR effect to allow their transport to tumors. Upon their extravasation through the leaky vessels, cellular delivery entails spatial binding of the loaded nanocarriers to the cancer cells and entering through receptor-mediated endocytosis mechanisms; the encapsulated drugs can be released to carry out their antineoplastic effect.

4.1. Factors affecting NPs' passive targeting of tumors

Passive targeting of tumors depends on the small size of NPs combined with the EPR effect feature of tumor vasculature (refer to Table 5). The successful accumulation of the loaded NPs' inside tumors is directly affected by the size, shape, stability, and surface charge of NPs as well as tumor type, stage, and perfusion rate, together with pores size in the leaky vessels and the level of pressure produced by the IFP. Passive targeting of tumors depends on the extravasation process of NPs through the leaky vessels surrounding tumors. This refers to the ability of NPs to transport blood vessels from the lumen into the interstitial space of tumors through the gaps between the endothelial cells making up the vessels. This process requires no energy and depends on NPs' concentration gradient as the higher concentration of NPs in the blood compared to tumor interstitium drives their passive transport (mainly through diffusion) across the endothelium, allowing their accumulation inside tumors [85]. Many factors affect the passive targeting process, such as NPs size. Only NPs with a size smaller than the cutoff size of the gaps in the endothelium will benefit from the EPR effect. Also, the continuous need for a large concentration gradient in NPs' concentration between the bloodstream and tumor interstitium means that high NPs' bolus doses are required. Additionally, NPs designed for passive targeting of tumors should be fairly stable while escaping from clearance by the reticuloendothelial system (RES) to allow longer circulation time to enhance NPs' extravasation. Generally, NPs' surface chemistry and net charge affect their circulation time, whereas hydrophobic and charged NPs are more prone to opsonization and clearance from the blood. Hence, modifying the surface of NPs to be "water-like" or more neutral and hydrophilic NPs enhanced their circulation time. To achieve this, NPs' surfaces are crafted with soluble polymers such as polyethylene glycol "PEG," a

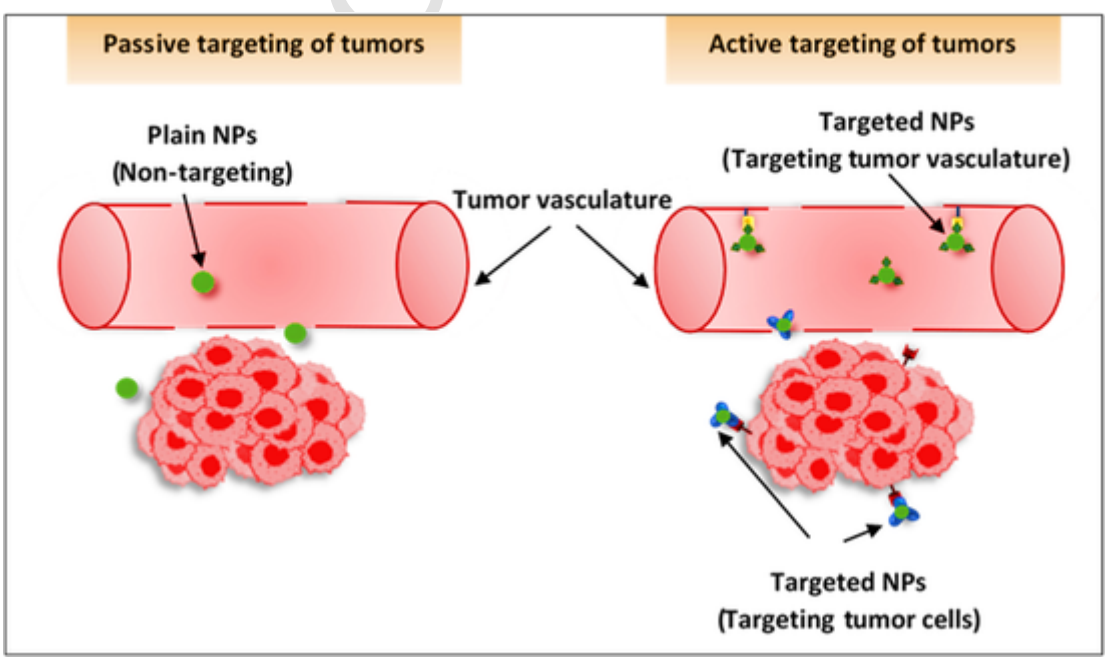


Fig. 4. An illustration showing plain NPs delivering drugs through passive targeting of tumors (non-targeting NPs) as well as active targeting of tumors using NPs targeting specific receptors located either on tumor vasculature or on tumor cells following their extravasation through the leaky tumor vasculature.

Table 5
Effect of size on active cellular uptake of NPs [98,100].

NPs	Diameter (nm)	Cell line	Findings	Ref.
Au	2-15	MCF-7	Smaller NPs were present in both the cytoplasm and nucleus. 15 nm NPs were only present in the cytoplasm	[101]
QDs	2-7	A-427	Internalization efficiency depended on the size	[102]
Au	2.4-89	Cos-1	2.4-nm NPs were present in the nucleus. 5.5, 8.2-nm NPs were present in the cytoplasm. No uptake for NPs ≥16 nm	[103]
Au	2-100	SKBR-3	40/50 nm NPs showed the highest internalization	[104]
Au	14-100	HeLa	Maximum uptake reported using 50 nm NPs	[105]
MSN	30-280	HeLa	Maximum uptake reported using 50 nm NPs	[106]
SiO_2	32-83	Caco-2	32 nm NPs were present in the nucleus and migrated faster	[107]
Polymer	50-300	Caco-2, HT-29	100 nm NPs showed the highest uptake	[108]
Ps	20-100	1321 N1, A549	40 nm NPs showed the highest uptake	[109]

process known as "PEGylation." PEGylation forms a protective hydrophilic layer around these NPs, resulting in enhancing their blood circulation time through spatial repulsion rejection [86]. PEGylation also significantly reduces NPs aggregation and non-specific interactions. Moreover, PEG polymers were found to be absorbed by epithelial membranes, and the size of the polymer significantly affects the rate as well as the mechanism of absorption [87]. However, PEGylation was also reported to slow the cellular uptake of some NPs [88]. To overcome this possible limitation, [89] developed enzymatically cleavable PEG-NPs, which use an enzyme present in TME to cleave the chemical bone between PEG molecules and the conjugated NPs; this resulted in producing PEGylated NPs with high stability during circulation and high cellular uptake. Conjugating PEGylated NPs to targeting ligands will also enhance cellular uptake of PEGylated NPs [90], which will be discussed in detail in the next sections of this review.

The high accumulation of NPs inside cancerous tissues compared to a significantly lower accumulation in normal tissue with no EPR effect results in reducing the associated side effects. There are several NPs-based drugs that have gained the approval of the U.S. Food and Drug Administration (FDA), for passive targeting of tumors, including liposome-base NPs (Doxil®, Abraxane®, Marqibo®, DaunoXome®, DepoCyt©, and Onivyde®), Protein-based NPs (Abraxane® and Ontak®), polymer-based NPs (Eligard®).

4.2. Active targeting of tumors: factors affecting cellular uptake of NPs

Active targeting of tumors plays an important role in delivering NPs loaded with chemotherapeutic drugs, genes, and theranostic agents specifically to tumors to reduce systematic toxicity and enhance therapeutic efficiency [53,91]. Active targeting-NPs can deliver higher quantities of drugs to tumors compared to passive targeting-NPs and free drugs. However, cellular delivery of loaded NPs can be challenging due to many obstacles facing their effective binding and internalization. For nanomedicine to be effective, a successful internalization into cells is important to achieve the intended therapeutic goals. The main strategies used by the different molecules to enter eukaryotic cells are membrane fusion, passive diffusion, and endocytosis. Membrane fusion occurs between two lipid membranes by lipid mixing and content transfer, such as liposome fusion with cellular membranes [92]. Passive diffusion requires no energy and is used by small non-polar molecules to move across cellular membranes. Endocytosis is the primary strategy used by most molecules, including NPs, to enter the cells. Generally, NPs are polar (charged) molecules and, thus, are unable to diffuse through cellular membranes. Instead, they are actively transported inside the cells through endocytosis. The two main types of endocytosis are phagocytosis and pinocytosis. Phagocytosis is used by the nonspecific immune system, such as macrophages, neutrophils, and monocytes, where cellular membranes are employed to engulf large-size particles such as pathogens and cell debris to be removed from the body. Small-size molecules, such as NPs, are taken up by all types of cells through pinocytosis which is a nonspecific process that occurs continuously regardless of cellular needs [93]. In pinocytosis, folds are created in the cellular membrane creating small pockets to capture extracellular and dissolved molecules. The main types of pinocytosis are caveolae-mediated endocytosis, clathrin-mediated endocytosis, clathrin- and caveolae-independent endocytosis, as well as macropinocytosis [94]. Understanding the factors affecting the cellular uptake of NPs is essential to establish their biodistribution, toxicity, and therapeutic efficiency.

During the process of clathrin-mediated endocytosis, particular molecules are allowed to enter the cell when specific ligands bind to receptors located on cellular membranes to form a ligand-receptor complex. Next, the formed complex moves to the clathrin-rich region of the membrane to be engulfed after clathrin-coated vesicles are formed [95]. Once inside the cells, protein coatings (clathrin coatings) surrounding the vesicles are disassembled, releasing the free vesicles, which then fuse to early endosomes to initiate the endo-lysosomal pathway [96]. Caveolae-mediated endocytosis, on the other hand, involves the formation of "caveolae" which are flask-shaped invaginations on the membrane (50-100 nm in diameter). Membrane caveolae are generally composed of detergent-resistant domains rich in cholesterol and sphingolipids, also known as "lipid rafts." Caveolae are abundant in endothelial cells, fibroblast cells, adipocytes and epithelial cells [97]. Following their detachment from the membrane, caveolae fuse with a cellular compartment (caveosomes) rather than the lysosomes. Thus, they protect their content from hydrolysis and degradation by the lysosomes, which makes caveolae-mediated endocytosis more suitable for the internalization of drug-loaded NPS [98]. For cells with membranes that lack both clathrin and caveolae, clathrin- and caveolae-independent endocytosis is used by utilizing other proteins, such as Glycosylphosphatidylinositol-linked proteins and interleukin-2 [98]. Generally, NPs ranging in size between 100-200 nm are internal-

ized into the cells via clathrin- or caveolae-mediated endocytosis [99]. Several studies have shown that 40-50 nm is the optimum size that shows the highest uptake by the different cells.

Together with the size, the shape of the NPs is equally important in determining their cellular uptake. For example, the shape and size of siRNA-conjugated gold nanoparticles were found to affect their uptake by glioblastoma cells, where larger particles in the form of sphere-shape (50 nm), and star-shape (40 nm) showed higher cellular uptake compared to the smaller sphere-shape gold nanoparticles [110]. The cellular uptake of nano-chemotherapeutics depends upon the angle of contact between the nanocarriers and the cell membrane. Filamentous micelles, nanorods, nanoneedles, or nanodisk-shaped nano-chemotherapeutics have shown a greater potential to target tumors as compared to spherical-shaped nano-chemotherapeutics, which show advantages with respect to ease in synthesis and development [111]. Zhou et al. [112] investigated the effects of the different shapes of nanostructures obtained by a self-assembly fabrication process, where the hydrophobicity of PEG-*block*-dendritic polylysine–camptothecin (PEG-xCPT) conjugates were manipulated to synthesize nanorods and nanospheres of different properties. The effect of the shape, length and dimensions of these formulations were investigated *in vivo* and *in vitro*. The results showed that the nanorod-shaped conjugates had more efficient cellular uptake compared to the nanosphere-shaped ones. Moreover, nanospheres and longer nanorods (>500 nm) exhibited low blood circulation dynamics and uptake as compared to the shorter nanorods. Therefore, cellular internalization, which dictates the efficiency of the pharmaceutical action of the encapsulated drugs, is a high function of NPs shape and geometrical properties. Similar work by Geng et al. [113] reported that the circulation time of paclitaxel-loaded filomicelles composed of PEG-polycaprolactone or PEG-polyethylethylene showed ten folds longer circulation time as compared to their spherical counterpart. The spherical NPs and short filomicelles (<4 μm) were more readily taken up by cells than the longer filomicelles (~18 μm), as the longer filaments in the presence of fluid swell and extend into long chains.

The surface charge of NPs also plays a critical role in facilitating their cellular uptake. The surface of NPs can be engineered to carry a positive, negative, or neutral charge. NPs surface can also be modified with a polymer coat, such as polyethylene glycol (PEG), or conjugated to a targeting ligand which also affects their overall charge. Cellular membranes are generally negatively charged, enhancing the uptake of positively charged NPs. However, the presence of positively charged NPs within cellular membranes may disrupt the integrity of the phospholipid bilayer leading to increased toxicity [114]. Brandenberger et al. [115] reported that while uncoated gold NPs were positively charged and taken up by the cells via macropinocytosis and clathrin and caveolae-mediated endocytosis, gold NPs coated with PEG were negatively charged and were internalized either through caveolae or clathrin-mediated endocytosis. Another study by Huhn et al. [116] examined the cellular uptake of gold NPs using different cell lines and concluded that positively charged gold NPs showed higher cellular uptake and toxicity compared to their negatively charged counterpart. Other studies have shown NPs with a neutral surface charge exhibited lower affinity to cellular membranes resulting in a significantly lower uptake by the cells compared to the negatively charged NPs [117,118].

Coating NPs with different types of polymers and functional groups can affect their interactions with cellular membranes. A successful functional group is expected to allow a safe and firm interaction of NPs with cellular membranes and their effective internalization into the cell. For instance, the functionalization of gold NPs with oligonucleotide resulted in superior cellular uptake compared to non-functionalized gold NPs [119]. Similarly, cellular uptake of poly-L-lysine fictionalized PLGA NPs was significantly higher than those without modification [120]. Liposomes functionalized with receptor-targeting ligands such as peptides, proteins, antibodies, and hormones were shown to enhance their cellular uptake [121–127].

4.3. Drug release from loaded NP: TME characteristics as intrinsic triggers of drug release

Both passive and active targeting strategies aim to achieve sufficient accumulation of the loaded NPs within tumoral boundaries [128]. As they accumulate in tumors, NPs can be designed to be responsive to one or more of the unique characteristics of TME, utilizing them as internal triggers of drug release (refer to Fig. 5). For instance, NPs can be responsive to acidic pH, elevated temperature, reactive oxygen species (ROS), hypoxia, reduced environment, and specific enzymes [129].

For example, amphiphilic polymer-based NPs can be designed to be responsive to the acidic TME by inducing the hydrophilic-hydrophobic switch. The polymer then becomes destabilized, allowing the release of loaded drugs under acidic conditions. Dalela et al. [130] Synthesized a copolymer poly (styrene-co-maleic anhydride), which was used to conjugate paclitaxel through an ester linkage and self-assembled to form PSMAC-PTX NPs. These NPs showed a high rate of paclitaxel release in acidic conditions. Moreover, These PSMAC-PTX showed a significant *in vivo* inhibition of tumor growth of Ehrlich Ascites Tumor-bearing BALB/c mice.

Another study by Zhao et al. [131] designed acid-sensitive PEGylated polyethylenimine linked through Schiff base (PEG-s-PEI) nano-assemblies that interacted with docetaxel and indomethacin. The docetaxel containing PEG-s-PEI nano-assemblies showed pH-dependent PEGylation cleavage under acidic conditions. They have the capacity to retain longer in the blood and are highly accumulated within the tumoral matrix. This smart pH-sensitive cleavage of NPs provided a new strategy to target tumors more efficiently. Min et al. [132] designed pH-responsive polymeric micelles using copolymerization of MPEG (methyl ether polyethylene glycol) and PAE (poly-beta-amino ester). The MPEG-PAE copolymer nano-sized micelles showed a sharp pH-dependent transition between micellization or demicellization at acidic pH resulting in an efficient release of their load. Xu et al. [133] developed ultra-pH-responsive polymers for RNAi-based tumor targeting and deep penetrating nanoparticles composed of a pH-responsive hydrophobic polymer (polyethylene glycol) and internalizing Arginylglycylaspartic acid (RGD). These RNAi-based nanoparticles (<70 nm) have shown significant gene silencing, which inhibited tumor growth with very low levels of *in vivo* toxicities.

As tumors grow, their heat capacity also changes. The shortage of oxygen supply to the growing tumor mass leads to hypoxia which triggers angiogenesis and exponential tumor cell growth and metabolism, resulting in the generation of energy and heat [134]. Studies have reported an average rise in the temperature of breast tumors to around 1.33 to 1.79°C compared to the surrounding

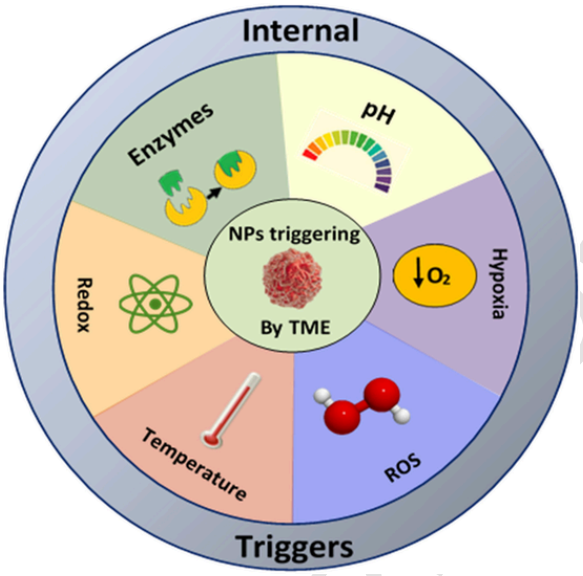


Fig. 5. The different characteristics of TME used as internal triggers for drug release from TME-responsive NPs

healthy tissues [135,136]. Both hypoxia and temperature have been employed in triggering drug release from NPs. For example, the hypoxic TME can be utilized to stimulate cellular uptake and drug release from PEGylated NPs by triggering PEG shedding from their surfaces. A research group [137] prepared hypoxia-sensitive PEGylated micellar nanoparticles (PEG-Azo-PEI-DOPE) or PAPD containing the hypoxia-sensitive "azobenzene" (Azo) as well 1,2-dioleyl-sn-glycero-3-phosphoethanolamine (DOPE) and polyethyleneimine (PEI) and units. PAPD NPs were co-loaded with a chemotherapeutic drug and siRNA. Once inside tumors, the hypoxic environment triggers the cleavage of the azo-linker resulting in shedding the PEG coat, revealing the positively charged PEI and subsequently enhancing cellular uptake of NPs. More recently, [138] used the same hypoxia-sensitive PAPD NPs to overcome the limitation of multidrug resistance (MDR) in tumors by inhibiting (silencing) P-glycoprotein (P-gp), which is an essential protein in inducing MDR, and producing significant cytotoxicity following the successful co-delivery of anti-P-gp siRNA and Doxorubicin (DOX) to the Adriamycin-resistant human ovarian cancer cell line A2780 and the MDR- human breast cancer cell line MCF7. Another *in vivo* study incorporated a hypoxia-responsive derivatized nitroimidazole (NI) into the phospholipid bilayer forming hypoxia-responsive liposomes. Upon reaching tumors, the hypoxic conditions lead to reductive metabolism of the NI disrupting the bilayer membrane. This resulted in releasing the encapsulated DOX showing higher cytotoxic efficiency with reduced systemic toxicity in the patient-derived xenograft model [139].

Temperature-responsive NPs are designed to be responsive to the rising temperature of tumor TME. External heating sources are usually allied to ensure a sufficient temperature increase. An example of thermo-sensitive NPs is the thermo-sensitive hydrogels, designed to be sensitive to a specific temperature known as "volume phase transition temperature" (VPTT). Temperatures lower than VPTT cause the hydrogels to swell, while temperatures higher than VPTT cause them to shrink, releasing their load of drugs [140]. Furthermore, several thermo-sensitive polymers have been developed and incorporated into different NPs to create thermo-responsive NPs able to retain their load during blood circulation but release their loaded drugs when exposed to a rise in temperature once inside the TME [141]. Another type of temperature-responsive NPs are traditional thermosensitive-liposomes (TTSL). TTLs are designed to maintain their intact solid/gel structure while circulating in the blood but transition into a more liquefied state (melt) upon their exposure to the local temperature of the TME. In addition, the structure of TTSL can be altered to enhance their sensitivity to temperature by incorporating thermosensitive phospholipid molecules (lysolipids) to create lysolipid thermally sensitive liposomes (LTSL). When heated, lysolipids create pores and areas of disorder in liposomal membranes during the phase transition process resulting in a higher drug release. ThermoDox® utilizes the LTSL technique to prepare thermosensitive liposomes encapsulating DOX. Upon a temperature rise to 40°C-45°C, the change in structure and pore formation result in releasing the encapsulated DOX. ThermoDox® showed significant enhancement of DOX delivery to tumors (25 times more compared to the free drug and 5 times more compared to traditional liposomes) [142].

4.4. NPs targeting tumor vasculature

Targeting tumor vasculature using loaded NPs facilitates drug delivery to targeted tumors without the need for passive targeting and the EPR effect. This allows them to target a wide range of tumors. The rapid proliferation rate of vascular endothelial cells results in the overexpression of several angiogenic markers making tumor vasculature an attractive target for drug-loaded NPs. Generally, endothelial cells are easily accessible for circulating NPs. In addition, they are genetically stable, sharing similar phenotypes across most tumors; thus, they can be used to target a wide range of tumors while reducing drug resistance. NPs targeting tumor vasculature

can be conjugated to different types of targeting legends, such as peptides and antibodies able to recognize and selectively bind to their targeted receptors overexpressed on the endothelial cells of tumor vessels. The loaded drugs can block angiogenesis either by disturbing tumor vasculature (vascular disruption) or by correcting the abnormal tumor vasculature (vascular normalization). Vascular disruption, through anti-angiogenesis, leads to total blockade of the immature and disorganized blood vessels by blocking pro-angiogenic pathways. Vascular disruption can also be achieved by inducing coagulation reactions by forming insoluble gels to block the vessels resulting in a reduction in the amount of oxygen and nutrients reaching tumors [25]. The vascular normalization strategy, on the other hand, aims to correct and normalize the abnormal tumor vessels to restore oxygen supply and enhance the delivery of therapeutic agents to tumors. This will also result in tuning the immunosuppressive TME, thus, restoring the function of anti-tumor immune cells and enhancing chemotherapeutic drugs' efficiency (refer to Fig. 6).

In this section, we will review NPs designed to target the receptors for important proteins which play a major role in facilitating tumor angiogenesis: integrins αv β3, CD105, and VEGFRs.

4.4.1. NPs targeting Alpha-v beta-3 ($\alpha_v\beta_3$)

$\alpha_v\beta_3$ receptors are a type of heterodimeric integrins consisting of two subunits α and β, and are found on cellular membranes. These integrins play an important role in cell-cell and between cells and extracellular matrix adhesion. They also play an important role in facilitating tumor metastasis by mediating cancer cell's invasion/migration and adhesion to other organs; thus, $\alpha_v\beta_3$ receptors are highly expressed in many tumors. When growing tumors are in the state of hypoxia, they send signals to recruit new blood vessels to increase the supply of oxygen and nutrients; these signals activate tumor endothelial cells, which line the interior of the tumor vasculature. $\alpha_v\beta_3$ integrins are usually highly expressed on the surfaces of activated endothelial cells and newborn vessels associated with tumors. In contrast, only a few are expressed on the inactive endothelial cells with limited tissue distribution. This makes them a suitable target for the different targeted NPs. Various nanoparticles have been used to target tumor angiogenesis for diagnostic and therapeutic purposes [143–145].

Murphy et al. [146] synthesized liposome conjugated to Cyclo(Arg-Gly-Asp-[D-Phe]-Lys) or c(RGDfk) peptide and loaded with DOX to target $\alpha_v\beta_3$ integrins overexpressed on the angiogenic endothelial cells (HUVEC). $\alpha_v\beta_3$-targeted liposomes showed a 15-fold increase in therapeutic efficacy and fewer side effects compared to the free drug. Peiris et al. [147] reported the usage of gold NPs to target micrometastasis (small cluster of tumors less than 2 mm in size). Unlike primary tumors, the early spread of metastatic cancer lacks the EPR effect; thus, NPs cannot extravasate the leaky vessels. To overcome this, the group developed gold NPs conjugated to the peptide c(RGDfc), to target and bind to $\alpha_v\beta_3$ integrins, which are upregulated in the tumor vasculature compared to the normal blood vessels. By modifying the nanoparticles to target the metastatic sites, 14% of the injected nanoparticles were accumulated at the target site within the first 60 min. These results suggest that growing metastatic tumors depend on angiogenic vessels and the important role $\alpha_v\beta_3$ integrins play in this process. Another Study [148] has also developed gold NPs coated with chitosan and surface modified with c(RGDfk) and loaded with the antiangiogenic drug "Sunitinib malate". Cellular studies on HUVEC and MCF-7 cell lines reported that the loaded NPs showed higher cellular internalization and higher toxicity compared to the free drug.

There are mainly two strategies used while targeting the tumor vasculature, one is to inhibit the angiogenesis, and the other is to disrupt the vasculature. Paris et al. [149] synthesize gold nanorods coated with mesoporous silica and decorated with RGDR peptide designed to target targeting tumor vasculature for the dual delivery of two anti-vascular drugs (Doxycycline and Fosbretabulin). The

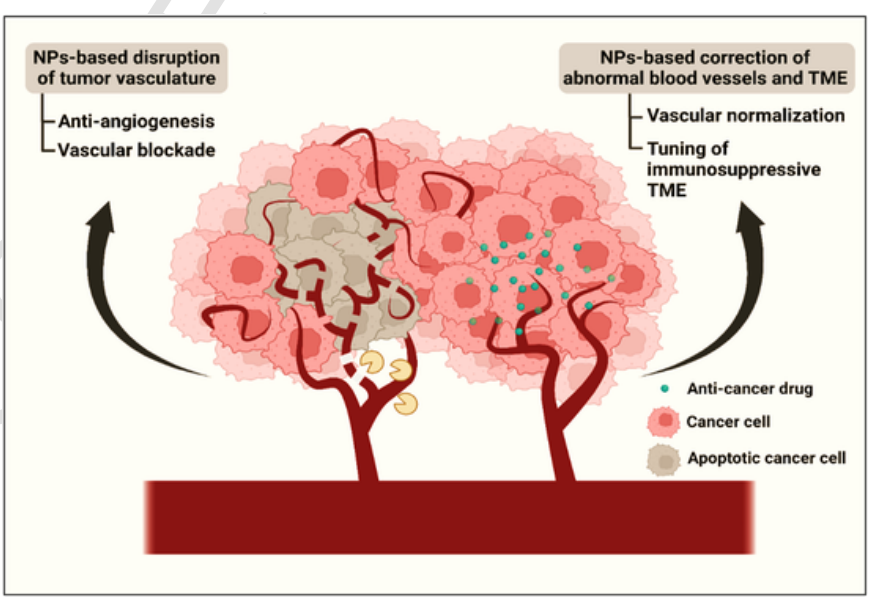


Fig. 6. Drug loaded-NPs targeting tumor vasculature to block angiogenesis by disturbing tumor vasculature (vascular disruption) or through the correction of abnormal tumor vasculature (vascular normalization).

targeted gold nanorods showed higher uptake by HUVEC cells. In addition, triggering the mesoporous silica coating with near-infrared light produced a thermal effect showing significant destruction of the blood vessels irrigating a fibrosarcoma xenograft model upon irradiation. These findings show the promising potential of delivering multiple drugs using a single NP targeting tumor vasculature.

4.4.2. Targeting CD105

CD105, also called endoglin, is a transmembrane glycoprotein, a growth factor (Transforming growth factor β) coreceptor, mainly overexpressed on the surfaces of activated endothelial cells during neovascularization. It has a significant role in angiogenesis, vascular remodeling and homeostasis and also binds to BMP-9 [149,150]. Compared to other vascular receptors, CD105 receptors are overexpressed up to 10 times more [150], which makes it an effective targeting moiety for tumor vascular imaging and therapy. Unlike $\alpha_v\beta_3$ receptors, CD105 receptors are homodimers, each unit of 95 kDa linked by disulfide bonds, making it a 180 kDa protein. The most studied antibody to neutralize CD105 is TRC105, which acts by preventing the binding of BMP-9. CD105 markers are also overexpressed in a wide range of tumor cells such as lung, breast, prostate, glioblastoma, and mesenchymal stem cells [151,152]. Therefore, NPs targeting CD105 can be used to target tumor vasculature and tumor cells. Targeting tumor vasculature has been studied for imaging purposes using various nanoparticles such as liposomes [153], Graphene [154], and mesoporous silica [155]. A review of its imaging applications can be found here [156]. This section will mainly focus on therapeutic NPs targeting CD105 receptors.

Huang et al. [157] synthesized small chain F_v fragment conjugated to PEGylated liposome able to bind to CD105 receptors delivering α1,3 GT plasmid to tumors; these plasmids can express αGal on the endothelial cells. The expression of αGal triggers the immune system and produces an inflammatory reaction that leads to acute vascular rejection. The antibodies generated by this process can completely remove the solid tumors to achieve complete remission. Yang et al. [158] designed platelet-like peptide NPs containing a sequence that binds to CD105 receptors transforming the endothelial cells into nanofibers. This provides sites for NPs to bind and transform into nanofibers. This amplifying process leads to forming artificial clots, blocking the blood supply, and inhibiting tumor growth. Treating triple-negative breast cancer, which is an aggressive form of the disease, is challenging due to the lack of targeting molecules on the tumor cells. The lack of overexpression can be circumvented by targeting the CD105 receptors over the tumor endothelial cells. Mu et al. [159] developed PEGylated iron oxide NPs coated with silica and conjugated to CD105-binding peptide to target CD105 receptors in both treat triple negative cancer cell and vasculature endothelium by targeting for the co-delivery of a chemotherapeutic drug (DOX) and an immune therapeutic agent (polyinosinic-polycytidylic acid). The synthesized NPs were able to induce apoptosis, inhibit tumor growth and improve survival rate in mice.

4.4.3. Targeting VEGFR

The vascular endothelial growth factor (VEGF) is dominant in new blood vessel formation and angiogenesis. VEGF is produced by cancer cells and binds to its multitude of receptors (VEGFR) located on the endothelial cells. This triggers a signaling cascade that promotes cell growth and migration from the existing vasculature [160]. There are different types of vascular endothelial growth factors, namely VEGF-A, VEGF-C, VEGF-D. VEGF-A, usually represented as VEGF, is the main growth factor released by the cancer cells to initiate angiogenesis and binds to VEGFR-2, whereas the growth factors VEGF-C and VEGF-D bind to VEGFR-3. VEGFR-2 is overexpressed in the majority of tumor endothelial cells, whereas VEGFR-3 are less in number and are mostly upregulated on endothelial tip cells, found at the tips of vascular sprouts. Strategies have been developed to employ targeted NPs to target these receptors and deliver anti-VEGFR drugs to tumor vasculature.

Goel et al. [161] used mesoporous silica NPs to deliver the anti-VEGFR drug "Sunitinib" to the mouse-bearing human glioblastoma (U87MG) cells by targeting VEGFR. PEGylated mesoporous silica NPs were conjugated to an anti-VEGFR-2 ligand "VEGF121" and a radioisotope "^{64}Copper" for imaging and therapeutic purposes. The results showed a three-fold increase in tumor accumulation for the VEGFR-targeted NPs compared to the non-targeted counterparts.

While VEGFR-2 is a popular target for nanomedicine, other studies have explored the benefit of targeting multiple members of the VEGFR family. For example, Annette Orleth et al. [162] developed a strategy to target both VEGFR-2 and VEGFR-3 receptors simultaneously. The group carried out an *in vivo* study using dual-targeted DOX-loaded liposomes conjugated to Anti-VEGFR2 and Anti-VEGFR-3 monoclonal antibodies. The results showed that dual-targeting of VEGF receptors produces higher therapeutic efficiency compared to the free drug (100 % vs. 80-90% reduction in tumor volume compared to free DOX treatment) in Rip1Tag2 transgenic mice.

Despite its promising potential, targeting endothelial cells using monoclonal antibodies was associated with a few drawbacks and limitations during clinical trials. This is due to the half-life of monoclonal antibodies; thus, frequent dosages are required to maintain their therapeutic window. Also, severe side effects were reported by the patients. To overcome these shortages, a promising approach to achieve a safer therapeutic suppression of angiogenesis is through the suppression of pro-angiogenic factors using small interfering RNA or siRNA delivered to endothelial cells using targeted NPs. A study by Egorova et al. [163] used polymeric nanoparticle "polyplexes" loaded with siRNA through electrostatic interactions between the cationic groups of the polymer and the negatively charged siRNA. The polymer was decorated with ligand targeting CXCR4 receptors overexpressed on the epithelial cells. The loaded siRNA targeted the expression of VEGFA, VEGFR1 and endoglin genes and resulted in efficient down-regulation of endothelial cells migration and proliferation. A recent *in vivo* study by Ho et al. [164] used cationic lipoplex NPs for targeted gene therapy prepared through the encapsulation of RBDV plasmid (pRBDV) that targets VEGFR and assessed its effect in mice with melanoma. Once transfected into the cell, this therapeutic gene expresses an anti-angiogenic molecule which then targets VEGFR contributing to a better therapeutic

efficacy compared to the free protein drugs. This therapeutic strategy provides a safer approach to increasing the concentration of anti-angiogenic molecules within TME.

4.5. NPs targeting tumor cells

Nanotherapeutics have revolutionized targeted drug delivery to cancer cells. Targeted NPs designed to target cancer cells provide a high level of precision and create a promising tool to deliver drugs and a wide range of therapeutic materials to cancer cells. Besides delivering drugs to TME, a more precise level of delivery is required for some cancer treatments. For example, some therapeutics need to be delivered at the organelle level, such as the nucleus, mitochondria, and lysosomes. This will maximize therapeutic responses to cancer treatment while minimizing the side effects of drugs designed to interact with the DNA, such as DOX, which causes oxidative damage to DNA and inhibits the topoisomerase II enzyme within the nucleus. Furthermore, cancer treatment, in the form of therapeutic genes, specifically targets the nucleus to exert therapeutic actions such as correcting missing or dysfunctional genes. Such therapeutics can be loaded inside NPs designed to actively target and bind to cancer cells to achieve successful cellular internalization and effectively deliver their payload to the interior of these cells. In fact, the first small interfering RNA (siRNA) was successfully delivered to humans using cell-targeting polymeric NPs [165].

NPs actively targeting cancer cells are prepared using different types of NPs decorated with an array of ligands such as peptides, proteins, antibodies, and carbohydrates. NPs targeting tumor cells take advantage of the EPR effect to allow their extravasation to tumors. They also take advantage of the highly expressed receptors on the surface of cancer cells by binding their targeting ligands to those receptors initiating their uptake by the cells via receptor-mediated [166]. Table 6 shows examples of different targeted receptors in tumors and their targeting legend conjugated to different types of NPs.

For example, delivering drugs to treat brain tumors, such as Glioblastoma (GBM) proved to be challenging due to the blood-brain barrier (BBB), which prevents the accumulation of drugs in the tumor. Therefore, NPs designed to target specific receptors overexpressed on the surface of GBM, as well as BBB cells such as transferrin receptors (TfRs) have been widely explored [167,168]. TfRs are responsible for importing iron into the cells and are highly overexpressed in GBM cells (up to 100-fold more than healthy cells) to meet the increasing demand for iron [169]. TfRs can be targeted using transferrin (Tf) or monoclonal antibodies as targeting legends.

The cluster of differentiation-44 (CD-44) is a cell surface adhesion receptor highly expressed in different tumor cells to promote metastasis. Hyaluronic acid (HA), a polysaccharide polymer abundant in the extracellular matrix (ECM), is one of the legends able to bind to CD-44 receptors. The CD-44 is highly expressed in multiple tumor entities such as lung cancer, ovarian cancer, hepatocellular carcinoma, and glioma [170,171]. Following the binding process with HA, the CD-44 receptor is activated and enhances the growth of cancer cells. HA is a large molecule and contains different functional groups (-COOH, -OH, and N-acetyl), which can be utilized to conjugate the molecule with different types of NPs. Several studies demonstrated that targeting CD-44 receptors via HA-coated NPs to deliver drugs to cancer cells is a promising therapeutic approach [172].

Folic acid (FA), a water-soluble vitamin, is one of the targeting molecules which specifically bind to folate receptors (FARs). FARs play an important role in the synthesis of nucleotide bases and are highly expressed on tumor cells with a limited expression on healthy cells; thus, they are one of the pivotal targeted receptors for drug delivery. Earlier studies showed that folic acid enters the cell through the receptor-mediated endocytic process [173]. Therefore, folic acid is repeatedly used in the synthesis of FA-NPs conjugates, promoting cellular uptake of these NPs through receptor-mediated endocytosis.

Among these is the human epidermal growth factor receptor-2 (HER-2). HER-2 receptors are overexpressed in 20-30% of breast cancer subtypes known as “HER-2 positive” breast cancer. HER-2+ breast cancers are generally aggressive, with a high proliferation rate and drug resistance, making them harder to treat compared to the other subtypes with low expression levels of HER-2 (HER-2 negative). NPs designed to target HER-2 receptors can significantly enhance breast cancer treatment. Several monoclonal Antibodies (mAb) have been widely explored as promising legends targeting specific biological markers, such as the humanized mAb Trastuzumab (Herceptin™), showing promising results during preclinical and clinical trials. For example, DOX loaded inside HER2-

Table 6
Different targeted receptors and their targeting legend conjugated to different types of NPs.

Targeting ligand	Targeted receptors	NP type	Cancers overexpressing these receptors
Folic acid (FA)	Folate receptors	ZnO NP [175], gold NPs [176], carbon nanotubes [177], liposomes [178], micelles [179], MOF [180], dendrimers [181]	*Breast cancer*, colon cancer, melanoma, lymphoma, cervical cancer, ovarian cancer, lung cancer and kidney cancer, brain cancer
Transferrin (Tf)	Transferrin receptors (TfR)	Micelles [182], quantum dots [183], liposomes [184], dendrimers [185], gold NP [186]	Brain tumors, colon cancer, pancreatic cancer, lung cancer and bladder cancer
Hyaluronic acid (HA)	CD-44	Liposomes [187], micelles [188], mesoporous silica [189], dendrimers [190], gold NPs [191], quantum dots [192], carbon nanotubes [193]	Melanoma, pancreatic cancer, lung cancer, ovarian cancer, colon cancer and stomach cancer
RGD/cRGD	αvβ3 integrin	Gold NPs [194], mesoporous silica [195], micelles [196], Fe_3O_4 NPs [197], liposomes [126,198], carbon nanotubes [199], quantum dots [200]	Colorectal Cancer, brain tumor, breast cancer and ovarian cancer.
Herceptin	HER-2	Liposomes [174], quantum dots [201], micelles [202], Fe_3O_4 NPs [203], gold NPs [204], mesoporous silica [205], MOFs [206]	Breast cancer

targeted PEGylated liposomes was found to reduce the cardiotoxicity associated with anthracyclines while enhancing their therapeutic potential [174].

Promising preclinical and clinical translation were achieved for targeted polymeric micelles loaded with Docetaxel and decorated with a peptide derivative (S,S,2,[3-[5-amino-1-carboxypentyl]-ureido]-pentanedioic acid) known as "BIND-014" able to target prostate cancer cells. *In vivo* results and phase I and phase II human trials showed that encapsulating the drug inside these targeted micelles resulted in an increase in circulation time, compared to the free drug, as well as low accumulation in the liver together with controlled drug release [207].

Antibodies are highly desirable as targeting ligands in preclinical and clinical trials due to their high targeting specificity. However, the use of full antibodies as targeting ligands can generate immunogenicity and the subsequent rapid elimination from the body. To reduce immunogenicity, full antibodies are replaced with fragment antibodies in some cases. HER-2-PEGylated liposomes encapsulating DOX were developed to enhance the therapeutic potential of the drug and reduce the associated cardiovascular toxicity [208]. Successful preclinical trials were followed by phase I human trials (MM 302) in patients diagnosed with advanced breast cancer. Other immune liposomes encapsulating DOX showed successful phase I and progressed to phase II human trials [209].

5. Concluding remarks

Chemotherapy is widely used to treat different types of cancer. While other forms of treatment, such as surgery and radiation, can only treat localized tumors, chemotherapeutic drugs are injected into the bloodstream, reaching primary tumors and tumors that have metastasized to other parts of the body. As chemotherapeutic drugs travel through the body, they attack fast-dividing healthy cells as well as cancer cells, due to the lack of selectivity, leading to several unpleasant and sometimes life-threatening side effects. Furthermore, most drugs have low aqueous solubility and face increasing MDR. Therapeutic SDDSs are promising therapeutic tools developed to overcome conventional chemotherapy's limitations. SDDSs can encapsulate both hydrophilic and hydrophobic drugs and significantly improve their biodistribution and availability while safely delivering them to targeted tumors which reduces their systemic toxicity and MDR. Furthermore, Nano-size formulations of SDDSs attracted increasing attention due to their small size and diverse properties. NPs can accumulate inside tumors either by "passive targeting" or "active targeting." Active targeting can be achieved by targeting different components of TME. Following their accumulation inside targeted tumors, a controlled and sustained release of the loaded drugs can be achieved. This review highlighted different NPs designed to target tumor vasculature as well as those designed to target cancer cells while employing the unique characteristics of TME as internal triggers to release the loaded drugs.

The high permeability of tumor vasculature and the EPR effect has been reported to facilitate the passive targeting as well as active targeting of tumor cells by allowing their accumulation inside tumors and their uptake by cancer cells [210,211]. However, the EPR effect is not a simple process since tumors are extremely heterogeneous, with tumors located on different organs producing different pro- and anti-angiogenic molecules, leading to diverse leakiness and thus, this may stop NPs from extravagating through the vasculature of some tumors. This limits the benefits of these types of targeting strategies to certain tumors with high proliferation rates and NPs with long circulation times [23]. Furthermore, The EPR effect is associated with high IFP together with complex ECM and chaotic TME. This makes it difficult for NPs to extravasate into tumors and reach all parts of the cancerous tissues regardless of the concentration of the loaded drugs [212,213]. In addition, the models used to validate the EPR effect may not necessarily represent clinical tumors. Generally, tumors in small animal models, often used to study drug delivery using NPs, are significantly different in structure and function when compared to human tumors, which makes the EPR effect more prominent in animal tumors compared to tumors in humans. While EPR effect in humans still plays a role in NPs accumulation inside tumors, the extent of this effect varies significantly depending on the patients as well as the type and stage of tumors.

The conjugating of ligands targeting tumor cells on the surface of the different NPs will surely enhance NPs binding ability and the subsequent cellular uptake by cancer cells. However, it will not increase their chances of reaching and accumulating inside tumors, making it impossible to predict the amount of NPs/drugs reaching tumors. Scientific research should be focused not only on improving the properties of loaded NPs to increase their circulation time but also on advancing our understanding of tumor vasculature. There is a growing interest in developing different pre-treatment techniques to enhance tumor vasculature permeability and allow NPs to fully benefit from the EPR effect. Several chemical and mechanical methods have been proposed to enhance the EPR effect leading to increasing NPs accumulation in tumors. For example, different vasoconstrictors and vasodilators are employed to enhance blood flow and enhance tumor perfusion. Mechanical effects, such as ultrasound, can enhance the EPR effect through the sonoporation effect, resulting in creating transient openings in cellular membranes [214]. Hyperthermia was also reported to enhance NPs extravasation through the leaky vasculature [215]. Radiation and photodynamic therapy (PDT) are promising modalities that augment the permeability of tumor vasculature by eliminating the well-oxygenated cancer cells located near the blood vessels, which act as a barrier that reduces the EPR effect [216,217]. Furthermore, the different types of NPs can be manipulated by modifying NPs size, shape, surface charge and surface coating to enhance their stability and modulate their extravasation through the leaky vessels.

Another limitation is that tumor cells do not overexpress the targeted receptors all the time, and thus, the density of the expressed receptors varies accordingly. The successful interaction between accumulating targeted NPs and cell receptors occurs when receptor density is high. Furthermore, the density of the targeting ligands conjugated to NPs also plays an important role in NPs-cell interactions. Generally, higher targeting efficiency is achieved when the surface density of ligands is high [218]. However, when ligands' density is too high, this results in increasing their steric hindrance [219]. Thus, a detailed investigation of the process of ligand binding to each receptor is necessary. In addition, the presence of targeting ligands on the surface of NPs may increase the chances of their opsonization and the subsequent clearance from the body [220]. Targeting folate receptors using FA-NPs is highly effective in deliver-

ing drugs to targeted tumors. However, when injected into the blood, high uptake by the liver may be observed due to the specific affinity between liver cells and folic acid, which causes hepatic toxicity [221].

NPs designed to target specific biomarkers overexpressed on tumor vasculature is another promising strategy. This is due to the fact that all solid tumors depend on angiogenesis which is a complex process and involves various components; thus, endothelial cells of all tumor vasculature overexpress the same types of biomarkers. Targeting these biomarkers allow NPs to deliver drugs to a wide range of solid tumors. In addition, those receptors are easily accessible and directly exposed to the functionalized NPs circulating in the blood, which eases the binding process without the need to go through the extravasation process and penetrate the gaps between the leaky vessels. In addition, tumor cells are more stable compared to cancer cells which mutate rapidly and develop drug resistance [222]. However, NPs-based disruption of tumor vasculature is linked to marginal tumor survival as well as tumor recurrence. This is due to the presence of mature/abundant blood vessels in the edge or periphery of tumors. In addition, external tumor cells are able to obtain oxygen and nutrients from the neighboring healthy tissues [25]. Furthermore, disrupting tumor vasculature results in elevating the level of hypoxia in TME and the subsequent enhancement of tumor aggressiveness [223]. A promising approach to address this issue is to employ targeted NPs to achieve combined therapy. Vessel-targeting NPs can be used for the co-delivery of anti-angiogenesis drugs, which disrupt tumor vessels, killing cancer cells inside tumors, together with toxic chemotherapeutic drugs that kill cancer cells located in the tumor periphery. In addition, NPs can also deliver a combination of chemotherapeutic drugs and vascular normalization agents, which help in restoring a normal blood flow to all cells inside tumors to ensure the delivery of chemotherapeutic drugs to all the cells [224].

The development of dual-targeting NPs that can target cancer cells as well as tumor vasculature represents a promising approach for targeted NPs. These NPs are able to bind to certain receptors which are overexpressed in both tumor cells and vasculature maximizing their tumor-targeting ability. Jing and workers [225] have developed nano-scale platelet vesicles encapsulating DOX and melanin nanoparticles and conjugated RGD to target αvβ3 integrin present in both tumor cells and vasculature and implement a chemo-photothermal elimination for both targets. Another study by [226] showed a promising and improved glioma targeting using PEG-poly(lactic acid) NPs decorated with the glycoprotein “Lactoferrin (Lf)” to target Lf receptors overexpressed on both glioma cells and the brain endothelial cells.

The majority of the available research in the field of Nanomedicine is focused on preparing NPs on a lab scale, whereas the more challenging scale-up of NPs production using conventional, physical and chemical, as well as, green biological methods, is still behind. There are several factors affecting the scale-up of NPs from bench to market, such as the type of materials used and their generally regarded as safe (GRAS). Furthermore, the size and shape of the NPs and their toxicological features together with their in *vivo* biodegradability, are also important factors [227]. Generally, the pharmaceutical industry largely adopts traditional methods to prepare NPs. However, these methods are often harmful to the environment because of the high usage of toxic reagents and the high energy demand. Therefore the used materials, solvents, as well as, the total cost and NPs’ development procedure need to be carefully selected. On the other hand, the green synthesis of NPs significantly reduces the harm to the environment and requires less energy while being equally effective as those produced using the traditional synthesis methods [228]. It is highly important that more research needs to be directed towards insuring that no changes in the physical and biochemical properties of the produced NPs occur during large-scale production and that the produced NPs retain their properties. Studies have shown that factors such as the velocity used during the mixing process [229] or the length of the sonication time [230] can directly affect NPs size during production. A safe and sustainable production process to produce high-quality, safe, stable and efficient NPs should be insured using scientific data [231].

In conclusion, the use of targeted NPs to deliver drugs to specific solid tumors represents a highly efficient delivery technique of anti-neoplastic agents. While targeting tumor vasculature seems less complicated compared to targeting tumor cells. Both strategies have advantages as well as disadvantages, continuing research efforts aiming to fully understand TME and develop more suitable NPs is essential to unlock the full potential of these drug delivery strategies. Tumors are generally diverse and thus, increasing the number of participants in clinical trials is highly important in understanding individual tumors to successfully develop NPs specially designed according to the patient's condition and the characteristics of the targeted tumors. Generally, stimulus-responsive NPs encapsulating multiple therapeutic agents and conjugated to more than one targeting ligand to be able to bind to different locations of the TME is a promising approach to treat tumors in the future.

Credit author statement

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Declaration of Competing Interest

None

Ethical Compliance

Not applicable.

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