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Cancer Stem Cells and the Tumor Microenvironment: Targeting the Critical Crosstalk through Nanocarrier Systems

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Abstract
The physiological state of the tumor microenvironment (TME) plays a central role in cancer development due to multiple universal features that transcend heterogeneity and niche specifications, like promoting cancer progression and metastasis. As a result of their preponderant involvement in tumor growth and maintenance through several microsystemic alterations, including hypoxia, oxidative stress, and acidosis, TMEs make for ideal targets in both diagnostic and therapeutic ventures. Correspondingly, methodologies to target TMEs have been investigated this past decade as stratagems of significant potential in the genre of focused cancer treatment. Within targeted oncotherapy, nanomedical derivates—nanocarriers (NCs) especially—have emerged to present notable prospects in enhancing targeting specificity. Yet, one major issue in the application of NCs in microenvironmental directed therapy is that TMEs are too broad a spectrum of targeting possibilities for these carriers to be effectively employed. However, cancer stem cells (CSCs) might portend a solution to the above conundrum: aside from being quite heavily invested in tumorigenesis and therapeutic resistance, CSCs also show self-renewal and fluid clonogenic properties that often define specific TME niches. Further scrutiny of the relationship between CSCs and TMEs also points towards mechanisms that underly tumoral characteristics of metastasis, malignancy, and even resistance. This review summarizes recent advances in NC-enabled targeting of CSCs for more holistic strikes against TMEs and discusses both the current challenges that hinder the clinical application of these strategies as well as the avenues that can further CSC-targeting initiatives.

Keywords Nanocarrier Targeting · Cancer Stem Cells · Tumor Microenvironments · Stemness Pathways · Stemness Biomarkers · Cancer Signaling

Introduction

Cancer Stem Cells in the Tumor Microenvironment

There is often a misconstrued perception of cancer as a singular, unitary mass when it is in fact an organ system of sorts, within which cells are recruited for transformation into malignancy. The interaction network that builds around these cells is what constitutes a tumor microenvironment (TME) and has a large variety of cells, both malignant and non-malignant, that act as nodes within this network, including endothelial cells, pericytes, myeloid cells, mesenchymal stem cells, immune cells and fibroblasts [1–3]. The extracellular matrix (ECM) is also heavily involved, with significant research pointing towards the ECM playing a critical role in intratumoral signaling, transportation, and immunogenicity within malignant tissue, solid tumors to be specific [4, 5]. The TME, in essence, is the cellular environment that is based around tumors or cancer stem cells (CSCs) and is responsible for the progression of the cancer within its host system, predominantly through its support for hyperproliferation.

Stem cells, on account of their tumor regenerative properties and their participation in tumorigenesis in terms of initiation and metastasis, are a key component of the TME for tumor progression [6, 7]. Cancer-associated fibroblasts (CAFs), one of the differentiated end-products of CSCs, are

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at the forefront of this tumor system-remodeling that aims to improve proliferative capacity, higher plasticity, and even drug resistance. CAFs manage to accomplish the remodeling as mentioned above via intercellular adhesion molecules (ICAMs) and cytokines like hepatocyte growth factors (HGFs), epidermal growth factors (EGFs) and interleukin-6 (IL-6) that promote cancer cell survival and proliferation while simultaneously pushing for progression of the tissue into metastasis [7–9].

One of the major reasons the TME is under such limelight when it comes to focusing target therapy is its role in tumorigenesis—a property attributed to it predominantly due to CSCs. In addition to generalized cancer progression, CSCs also induce traits of drug resistance and regenerative capacity in tumor cells that are the primary causes of ineffective clinical trials for cancer [6, 10, 11]. Furthermore, CSCs regulation is heavily ingrained in interaction with their corresponding microenvironments. Research points towards cancer cells getting triggered into displaying resistance and other stem cell-like properties as a result of certain environmental conditions [12]. Such trials have been used to identify environmental markers that bring about the unwelcome traits of resistance and tumor progression in oncotherapy which allows for treatments to be more directed and niche-specific in their approach.

CSCs have been unquestionably established as playing a central role in the setbacks currently faced in clinical trials and pre-clinical research. Thus, devising a system that can target them at both a cellular and systemic level within the TME is the most promising of the presented avenues in the evolution of therapeutic design. By reviewing nanoparticular drug delivery systems (DDSs) targeting a variety of CSC niches that present genuine potential in clinical implementation, this paper aims to both address the shortcomings in current DDS designs when it comes to CSC targeting and provide a scaffold on which a multi-fronted format of cancer therapy can be supported.

Nanomedicine and its Applications in Cancer Therapeutics

Nanobiotechnology may have various applications in other fields of science, but some of its most significant applications remain within the pharmaceutical and biomedical sciences, where current study has significantly progressed conventional systems of drug delivery [13, 14]. As a field, nanomedicine has progressed so far from its roots of a novel application in the current stream of therapeutics that the US National Cancer Institute (NCI) was able to withdraw funding for the Center of Cancer Nanotechnology Excellence (CCNE), confident that the field was well enough established to be self-standing [15].

While its most promising domain of application remains cancer, nanomedicine also shows a great deal of potential in varying fields of medicine: their ability to pass through the blood–brain barrier (BBB) via either transcytosis or endocytosis allows nanomedicines to implement highly efficient treatment to the central nervous system (CNS) and any of the diseases that plague it. There are several preclinical trials of nanomedicine with animal models of brain diseases, including gliomas [16], Huntington's [17], and even Alzheimer's [18], with a particular focus on transcytosis, which enables passage of not just smaller molecules but also nucleic acids and proteins, in a non-invasive manner [19].

Reverting to oncotherapeutics, the predominant effort in the ongoing battle against cancer has always been in its eradication, in complete cure. However, it is just as important to consider the process from the patient's perspective. The current regimen of chemotherapy, immunotherapy, and radiation is painful and invasive, and it makes the road to recovery an extremely uncomfortable one. While complete cure will always be the ultimate goal, improved life quality of the patients on the receiving end of this treatment is also a matter that needs to be urgently addressed [20]. This therapeutic sector is where nanomedicine shows the greatest promise—in non-invasive reorganization of the current regime [21].

As for the nature of its applications, nanomedicine forks into two approaches on how it can enable improvisations in current cancer therapy: it can either create an entirely new drug to target cancer in a highly specific manner or better the specificity of current delivery models [18, 19]. The focus of this review will be on the improved administration of pre-existing drugs.

Carriers in Nanomedicine for Drug Targeting

Nanoparticles (NPs), on account of their size and unique properties (volume-to-charge ratio), act as a link between bulk matter and its composite molecular and atomic structures. Some of the major contributions of nanobiotechnology within medicine are in disease diagnosis and target-specific drug delivery [11]. Therapeutic approaches include drug delivery where NPs can either be applied as therapeutic particles or as casings for the intended drug. They are typically involved in tissue and cell level interactions, and their biggest application is as carriers of active drugs in drug delivery models so as to ensure specific release of the active drug and its extended maintenance within the patient's system [22–24].

These nanocarriers (NCs) are particularly advantageous in the medical field because a large degree of the scopes currently employed for detection technology development trigger the body's immune response [23, 25, 26]. Consequently, drug targeting is an especially important application

when it comes to cancer cell systems. Widespread treatment regimens (chemotherapy, immunotherapy) are designed to kill cells in the tumor vicinity and thus, run the risk of harming or altering healthy cells in the process. To overcome this issue, drug specificity to the tumor cells becomes paramount. An important advantage of NC employment is that it is non-invasive while also being capable of accessing deeper tissues and can be precisely controlled and focused onto specific target sites [27, 28].

Extending beyond just drug administration, NCs also present potential for in vivo long-term tracing systems specific to CSCs, most popularly in the form of metallic NPs [29–31] and fluorescently labelled aggregation-induced emission (AIE) dots [32]. Such applications, while important as preventive measures against secondary cancers borne from metastasis, also allow for closer insight on the details of the role and interactions of CSCs within the TME.

TME and CSCs in Cancer Metastasis and Drug Resistance

It is now a well-established fact that cancer is significantly harder to treat once it begins metastasizing, with almost 90% of cancer deaths being accounted to metastatic tumors as compared to primary tumors [33]. Not only does the TME play an integral role in the progression of a cancerous cell into metastasis, but the change to a TME once the tumor is settled at a secondary site is also a major factor to ponder when answering the question of why metastatic tumors are far more lethal than their primary brethren [34].

Microenvironmental Involvement in Metastasis

The 'how' of TME involvement in cancer metastasis is now relatively well-established. A plethora of TME cells, including CAFs, immune-inflammatory cells, adipose cells, and neuroendocrine cells (NECs), interact with the blood and lymphatic networks to create a self-propagating system of excessive proliferation, tumorigenesis, and metastatic growth. This network in turn is regulated by a large number of cytokines and chemokines, including but not limited to platelet-derived growth factors (PDGFs), vascular endothelial growth factors (VEGF), fibroblast growth factors (FGFs), transformation growth factors (TGFs) and their corresponding receptors [35–37]. While the TME does differ vastly depending on the cellular histology and the location of a tumor mass, the most cardinal—and by extension, the most common—TME cells are CAFs like adipocytes [38 39], myofibroblasts, and mesenchymal stem cells (MSCs) [9, 40, 41]; immune-inflammatory cells like regulatory T (Treg) lymphocytes, B lymphocytes, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs) [42, 43] and neutrophils [36]; angiogenic vascular cells like pericytes [44]; and other miscellaneous cells like NECs [8] and dendritic cells (DCs) [3, 42]. Given their involvement in several cancer hallmarks, these cells then form the basis of primary targeting employed in all the current forms of cancer therapy, depending on their functional influence pertaining to a particular form of cancer.

Aside from considering the TME's effect on cancer progression, the differences between metastatic and primary TMEs, as well as their corresponding influence on cancer invasion, must also be taken into account [45–47]. Their perceived role in the aggressive nature of metastasized cancer is yet another reason TMEs should be viewed as ideal targets in cancer therapeutics. Following the Paget theory of 'seed and soil' in 1889 for metastatic spread, it has been an increasingly circulating notion that the TMEs of metastases are bound to be distinct from that of their 'seed' (the primary tumor) despite both the cells being of the same histological origins. While the environment of the secondary site does play a role in this differentiation, there is also involvement of the interactions a circulating tumor cell (CTC) undergoes when migrating towards a parenchymal site among distant tissues [34, 36]. Upon intravasating into the blood stream as either individual cells or multicell clusters, CTCs' interactions with neutrophils and platelets become a means of progressing tumor metastasis as they respectively facilitate extravasation and prevent both tumor cell recognition as well as lysis from NK cells [36, 48]. Other interactions involve macrophages, MDSCs, and lymphocytes and cumulatively converge around the final goal of CTC invasion and the establishment of a secondary site [34, 48–50], as compiled within (Fig. 1).

A cross-cancer comparison of primary and metastatic ovarian tumors was able to profile some characteristics that distinguished the two corresponding TMEs. On account of metastatic growth, tumor cells developed a higher density of TME cells with disease progression and resulted in better regulation of malignant-cell derived chemokine and cytokine networks (with IL-16 playing a crucial role in their orchestration) [51]. There was also an increased concentration and alignment of collagen bundles within the neighboring ECM, as well as a close correlation between tissue stiffness—and by extension, cellular rigidity for better survival—and disease progression. The same index was also cross-referenced against other cancers and definitively concluded that ECM-associated gene expression in connection to the matric index was applicable across all human cancers [52]. Aside from this, a clinical study on luminal breast cancer differentiation between primary and metastatic sites validated the immune component of the TME cells mentioned in the above review by establishing the bearings for a potential bridge between metastatic TMEs and cancer relapse [47]. It insinuated that verified lower tumor-infiltrating lymphocyte (TIL) concentration at metastases, due to increased cell density at the

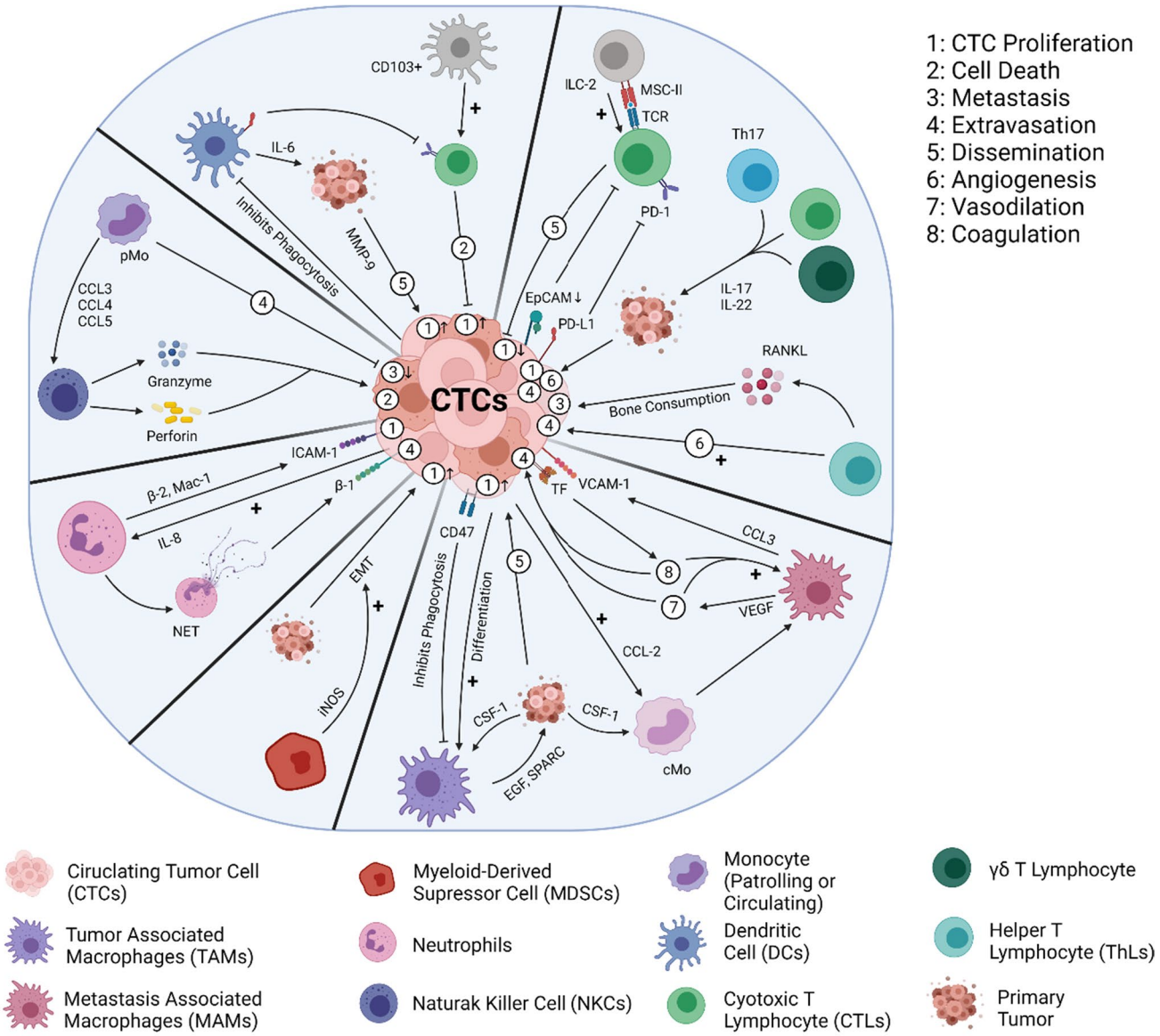

Fig. 1 CTC interactions during the metastatic process. The above figure details the varying interactions that CTCs undergo, alongside their potential contributions towards the differentiation of the secondary TME from its pre-metastatic state. Out of these interactions, those with the immune aspects of the circulatory system seem to have the greatest impact on the TME's characterizations between primary and secondary metastases [49]. (Created with BioRender)

secondary site, could be linked to a reduced autoimmune response as well as other conditions encouraging overall survival and relapse [47, 51, 53, 54].

The TME's involvement in all aspects of tumor growth and progression, extending as far as relapse, makes it the optimal target when considering prognosis. However, with directed treatment arises the issue of TME differentiation between cancer types and sub-types, which would require painstaking studies and profiling of TMEs for all the varied cancers and their corresponding metastases at different parenchyma. While this method is wholly valid and effective, a more efficient approach would be to identify and isolate a keystone element within the network that would afford a greater wield of control over the TME as a whole—and this is where CSCs come to play.

Stem Cells as a Point of Origin for Cancer-Associated Tumor Microenvironment Cells

There are many brands of thought on the origins of TME cells; the two most common are that these cells originate from the neighboring tissues [55] or that they originate from cancer cells [6]. While the most likely model is a hybrid of the above two approaches, the focus of this paper

is on CSCs. They are a self-renewing cell type responsible for the maintenance and proliferation of tumor tissue as well as metastatic initiation, and can even differentiate into various TME components through stem cell pathways, like Notch, Hedgehog, Wnt, and TGF-β [56–58].

As such, there are predominantly two models for CSC contribution to tumorigenesis—namely the classical model and the plasticity model [59–63]. In the context of the former, variegated cell phenotypes in a TME are primarily the result of CSC differentiation after a microenvironmental alteration [59, 62]. The plasticity model builds on the foundation of the classical model and addresses the interchangeable conversion between differentiated adult cells and CSCs. While CSC differentiation into non-CSCs is well characterized via stem cell pathways, stemness transcription factors like Oct-3/4, Klf-4, Sox-2, PI3K [64, 65] as well as epigenetic regulations like DNA methylation/demethylation at CpG islands, histone modifications, nucleosome positioning in correspondence to the above genes [66] also help revert an adult cell into induced pluripotent stem cells (iPSCs) [67, 68]—thus the model's nomenclature. The interchangeable maintenance between CSCs and non-CSCs within the TME suggested by the plasticity model goes a long way in explaining CSC robustness, as it likens to the benefits of genetic variation for a population's survival initially proposed in Darwin's theory of evolution [61, 62, 68].

Both these models prescribe to the overarching hierarchical model of tumorigenesis, which assumes a progenitor between adult stem cells and actual tumor heterogeneity in CSCs [59, 62, 63]. However, most cell populations within the TME seem to adhere to the stochastic model of random mutagenetic accumulation [57, 60, 62]. Here, heterogenic tumor cells have been hypothesized to be induced from chronic inflammation or from conditions wherein normal stem cells or progenitor cells are induced through mutagenesis to become cancerous [7, 59]. Currently, in clinical conditions, iPSCs hold the most potential in the direct generation of CSCs [59]. CSCs derived from iPSCs reprogrammed from normal cell lines could differentiate into multiple tumor components, including CAFs, TAMs, adipocytes, and tumor-associated endothelial cells (TECs) [7]. While the pathways of CSC differentiation aren't entirely mapped out and are bound to be questioned for validity, there is definitive proof that CSCs can differentiate into CAFs [7, 69]. CAF involvement in tumorigenesis, cancer progression, and drug resistance by induced heterogeneity [70–73] alone should be sufficient reason to seriously consider CSCs as a target in oncotherapy, especially considering how stromal cell targeting has already shown results in overcoming chemoresistance [74, 75]. A review of the graphical abstract would better highlight the (quite literal) central role that CSCs have in TME-supported cancer progression, which in turn marks them as 'keystone' targets, capable of bringing the entire tumorigenesis pathway to a stalemate if hit successfully.

Stem Cell Involvement in Tumor Microenvironment Regulation

In addition to being a core contributor to the various cellular sub-populations that comprise the TME, CSCs are also heavily involved in the regulation of the microenvironment via a plethora of their characteristics. Some of the core behaviors that characterize CSCs are deregulated hyperproliferation, resistance to cell death, hypoxic autophagy, ferroptosis, increased angiogenesis, and increased induction of metastasis [58, 76–78]. CSCs attain excessive levels of self-renewal through participation in stemness pathways, including Hedgehog [79–82], Notch [83–87], Wnt/β-catenin [83, 88, 89], Nanog [90–92], NF-kB [93, 94], RAS [95, 96], p38 MAPK [97–100], PI3K [100–102], and EGFR pathways [103–105]. As has been elaborated, CSC participation in these pathways is key to its differentiative capacity and overexpressed stem pathways can be associated with biomass growth in tumors [58, 106, 107].

Increased vasculature is another characteristic of CSCs that involves heavy cross-activity with the TME [8, 108, 109]. Angiogenesis is an important part of microenvironmental maintenance and also plays central role in immune evasion, hyperproliferation, metastasis, and therapeutic resistance [5, 110–116]. Moreover, CSC-initiated angiogenesis via factors like VEGF, Ang-2, MIP-2, TGF-β1, IL-6, and IL-8 as well as vasculogenic mimicry are also regulated by stemness pathways [111, 117–119]. Angiogenetic factors like the von Willebrand factor [120–123], Tspan-8 [124, 125], the chemokines CXCL5 [126–129] and MIF [130–133], the CCR chemokine receptor family [50, 134–136] are often mediated through exosomes to ensure vascular up flux and endothelial regeneration [111–113, 137]. The ECM, a core element of the TME, also plays a critical role in determining proliferative tendencies during angiogenesis as well as regulating CSC differentiative capacity by impacting cellular stiffness [4, 5, 114, 138].

One of the most impactful ways CSCs interact with the neighboring TME is through their modulation of hypoxia [51, 57, 139, 140]. The result of a cellular proliferation rate that can no longer be supported by the transfer rate of oxygen from blood, hypoxia's key presentations include suppressed apoptosis [141–144], progression of EMT [144–148], malignancy and distant tumor metastasis [141, 142, 149–152], and deregulated angiogenesis [139, 153–155]. Hypoxia regulates on the basis of hypoxia-inducing factors (HIFs) and their interactions with stemness pathways, transcriptions factors, and other cancerous agents [152, 155, 156]. Pillar interactions include HIF-1α with TGF-β1 via a SMAD-dependent pathway [157–161] or with Notch-1 [162, 163] for hypoxic

initiation of EMT, with VEGF [164–166] for angiogenic regulation, and with GLUT-1/3 [167, 168] and hexokinase (HK)-1/2 [169–172] for a shift towards glycolytic metabolism [169]. Other common associated markers include LOX [173–175], MMP [173–175], Twist [176, 177], STAT3/IL-6 [178–183], MAPK/ERK [184–186], Sox-2 [187–190], Oct-4 [191–193], and c-Myc [194–197]. While the HIF family remains the primary mediators of the hypoxic response, research also points towards exosomal involvement in various hypoxic functionalities [151, 198–201]. Given their vesicular nature, exosomes' involvement in the TME does shine light on the possibility of their usage as next-gen NCs, specifically in the context of CSC-targeting.

The plasticity model clearly establishes a horizontal axis of differentiation between CSCs and non-CSCs, with the implication that inter-differentiation is the primary cause of cancerous cellular tendencies. Yet, there is evidence in traced lineages indicative of stochastic growth patterns in tumor tissue [202]. This indicates a sensitivity to the microenvironment suggestive of a feedback control loop in CSC maintenance [63, 65, 202]—in fact, TME regulation of CSC plasticity has even been linked to regulated quiescence [203, 204], which is central to immune escape [110, 205] and metastatic initiation in CSC and other tumor-initiating phenotypes [204, 206, 207]. Quiescence-induced tumorigenesis during immune-compromised conditions as well as the endowed immunosuppressive properties also contribute towards CSC-mediated chemoresistance [203–205, 208].

Given the highly involved interconnection between CSCs and the TME, the relevance of a multi-fronted targeting mechanism that can initiate anti-cancer activity at both a cellular and microenvironmental scale becomes significantly more promising in enabling non-recurrent cancer recovery.

Stem Cell Heterogeneity and Drug Resistance

The CSC theory holds that tumor growth is fueled by specific stem cells. The corresponding model is also based off four key features: cellular heterogeneity, self-renewal, limited plasticity within tumor hierarchy, and drug resistance [209]. The multi-drug resistance phenomenon that currently plagues all cancer therapy is on account of CSCs, induced by endogenous detoxifying enzyme expression, higher levels of drug efflux, decreased drug response, hypoxic stress on the TME, or even increased DNA repair activity [31, 210–213]. The mechanism of CSC drug resistance is via stem cell pathways. They express ATP-binding cassette (ABC) transporters, which are multi-drug resistant and can eliminate potential for drug damage. Even if the cells undergo some degree of injury, certain CSC markers like stem pathways also help negate oxidative stress by removing free radicals and induce resistance to chemotherapeutic drugs. CSCs also activate DNA repair capabilities within tumor cells, which contributes towards protection against apoptotic factors [58, 209].

Cancer drug resistance at a tumor level is enforced predominantly through two phases of rejection—the tumor can either be intrinsically resistant or develop resistance through positive selection of an unaffected subpopulation [73, 212, 214]. Given CSC involvement in the cellular and biomolecular make-up of tumors from initiation to metastasis, they by default become the focus of therapeutic resistance: they contribute both the cancer-associated cells that characterize innate resistance as well as the heterogeneity and survival mechanisms in the form of stem cell pathways that ensure sustained tumor proliferation and evolution [215, 216]. These very mechanisms also go on to increment an eventual trigger for a relapse in the disease [216].

Current Regimens for Cancer Therapy

Targeted delivery systems were developed primarily to address the need for regulated concentrations of drugs to be administered long-term. Initial systems were characterized by immediate release upon entry into the system. Thus, the compound would be partially or fully metabolized before it could reach the actual terminus, leading to both reduced efficacy of the treatment and risks of side-effects from metabolic by-product accumulation in non-related organelles [217]. Targeted delivery systems comprise the active drug being introduced directly into the organelle in question, with minimal widespread release. The drug's design, then, no longer has to bear in mind any interactions it will partake in before it reaches the target cell or tissue and can instead hone more towards amplifying anti-tumor activity.

Cancer-Specific Drug Targeting Therapy

The two streams of targeted delivery have remained consistent over the past decade, with the major variations being limited to only the targeting mechanisms and the delivery vehicles. The principle of the delivery itself remains preserved. These two strategies are namely active and passive targeting systems.

Passive targeting in cancer is characterized by its use of the anatomical and functional differences between normal and tumor vasculature to ensure a selective accumulation of drugs at the tumor site, dependent on enhanced permeability and retention (EPR), impaired lymphatic drainage, and localized delivery [218]. The EPR effect enables smaller compounds to accumulate far easier in tumorous tissues than healthy ones due to the former's heterogeneous vascularity and highly permeable membrane: this in turn ensures a modicum of tumor-selectivity within the delivery mechanism so that minimal healthy cells are tampered with. Localized

delivery, on the other hand, involves direct delivery of the drug to a specific tumor site to exclude the systemic side effects of the drugs while also concentrating drug levels at their site of action [218–220].

Active DDSs are designed upon the basis of specificity to either vascular endothelium or tumor cells by making use of affinity ligands. Endothelium cells are ideal targets as they are easily accessible through circulation, are genetically stable, and tend not to develop resistance against therapeutic agents. Further, they are easier to mark on account of the angiogenetic processes that they undergo, wherein the development of new blood vessels in tumor tissue to meet nutritional requirements results in activated endothelial cells that show elevated expression of adhesion molecules and proteolytic enzymes [221, 222]. In the case of tumor cells, several proteins are overexpressed in comparison to healthy cells and can serve as significant biomarkers for the progression of the disease and as surrogate markers for an indirect measure of drug therapy efficacy. These above-mentioned biomarkers, preferentially expressed in cancer cells, are also known as tumor-associated antigens (TAA). Aside from TAA-based targeting, tumor cells are also an ideal locus of targeting given that they present cell-surface receptors (CSRs) to a higher degree for increased nutrition influx, which also makes for easier drug uptake. Aside from surface CD markers, the most commonly presented receptors to induce intake are folate receptors, LDL receptors, and hormone receptors [217, 220].

One way of looking at these two targeting systems is as a sequence, as depicted in (Fig. 2). At its essence, the principles of active delivery ride on those of passive targeting: in both systems, the localization of the NC to the target tissue is through the circulatory system, by taking advantage of the 'leaky' vasculature—gaps in the endothelial lining of blood vessels that result from poorly controlled angiogenesis and subsequent EPR [217, 220, 223]. The difference is solely on the basis of specificity. Passive targeting uses EPR as its selective mechanism, which active targeting incorporates to further hone in on a tumor niche in particular. Between the two, active targeting is preferable for cancer-based applications simply because EPR isn't a selective enough factor to base the targeting of chemotherapeutic agents over. This is even more applicable in the case of metastatic malignancies that aren't established enough to be subject to EPR. A literary survey of NC-delivery to solid tumors spanning the past decade reported a median of 0.7% for the percentage of successful targeting [22]; even if this degree is significantly higher than the efficacy of free drug administration, at face value such a low degree of efficiency does bring into question the validity of the EPR effect as an efficient target.

A particular development in NCs as vehicles for active targeting is the concept of stimuli-responsive drug release. This is applicable in both passive and active mechanisms of targeting but serves its purpose better for active targeting applications. There is no control over the drug compound once it has been liberated, so having stimuli-responsive release doesn't necessarily contribute to the specificity of passive delivery. Because the CSC markers commonly targeted during active delivery are often involved in endocytic mechanisms [221, 222], the drug release in such contexts happens within the target cell, where no further control over the compound is necessary. Overall, their capacity to enable "on-demand" drug distribution that is spatiotemporally controlled makes these stimuli-responsive NCs an extremely

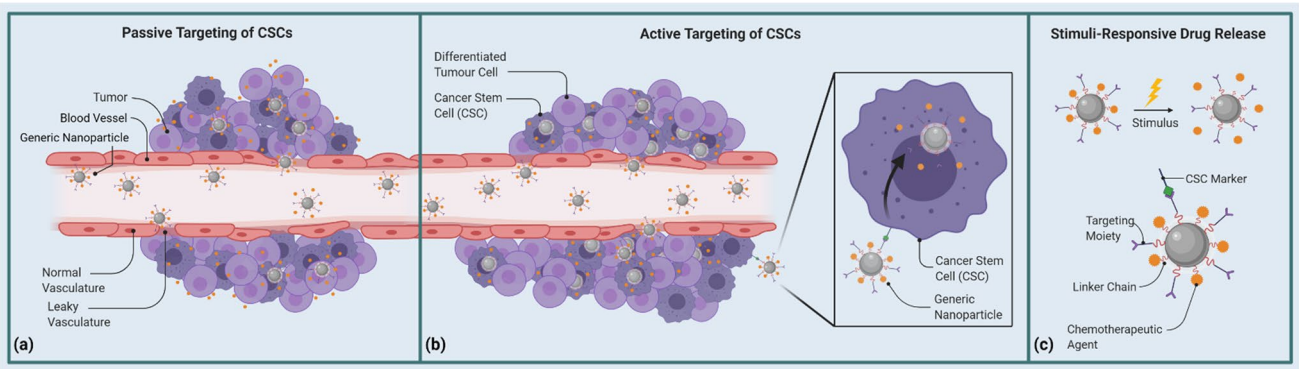

Fig. 2 Principles of active and passive targeting for targeted drug delivery as well as stimuli-responsive drug release. **a** Passive targeting of CSCs, **b** Active targeting of CSCs, **c** Stimuli-responsive drug release. The above panel elaborates on the two main methodologies of targeted drug delivery to CSCs within tumors, namely active and passive targeting. It shows how passive targeting (a) is the basis over which active targeting (b) is a more specific overlayer. It approaches the tumor in the same manner as passive targeting, by taking advantage of the circulatory system and points of distorted endothelial lining near tumoral bases. But the actual biodistribution of the drug is intracytotic, made more direct to CSCs by engaging specifically with markers exclusive to particular CSC niches. This specificity is further enhanced by the mechanism of stimuli-responsive drug release (c), which caters to a spectrum of internal and external stimuli. (Created with BioRender)

attractive solution to the issue of premature release within encapsulated delivery models. Among such NCs, the "sensitive" aspect is typically attributed to the linker chain holding the chemotherapeutic agent to the main body of the carrier. The stimulus induces either protonation, hydrolytic cleavage, or a molecular conformational rearrangement of the linker [224], all of which essentially block the site adhered to the anticancer agent, thus resulting in the latter's biodistribution. As such, controlled release is a highly applied feature in NC-mediated drug delivery, in response to a plethora of stimuli both external and internal, including magnetic fields, electronic fields, heat, light, ultrasound for the former and pH, redox, hypoxia, enzyme activity for the latter [224, 225]. To make the stimuli-responsive system even more attuned to TME-specific interactions, a proposed multi-stimuli tactic specific to the internal stimuli set of hypoxia, enzymatic regulation, redox, pH, and ROS also holds a degree of popularity [226].

Nevertheless, it is something to note that despite targeted delivery showing immense success in pre-clinical studies, there has been very little turnover in these NCs being employed for clinical use. Even out of the ones that have made it past clinical trials, there is no incidence of an actively targeting NC [227]. One potential reason for such nominal biocompatibility can be the several physiological barriers that NCs are faced with, including endothelial barriers during extravasation, potential degradation from endocytic pathways, the escape of endocytosed NCs from the endo-lysosomal system because of vesicles, and even mononuclear phagocytic system (MPS) clearance, all of which significantly reduce the efficiency with which NCs can home their deliveries [223, 227]. These issues, however, can be bypassed via localized delivery, which essentially affords simultaneous control over the location of release, compound diffusion rates, and even duration and retention of both the release and the compound [227]. As for the low turnover rate of NCs, several meta-analyses of NC translation from in vitro to in vivo environments indicate as markers of successful biotransitions the fair correlation between the two models for hemolysis, coagulation, complement activation, opsonization, phagocytosis, immunosuppression, and thrombogenicity, albeit in the context of immunotoxicity alone [228]. But because there is no definitive correlation between in vivo and in vitro set-ups for the above factors, translating NC-based systems to in vivo environments becomes too unpredictable to be clinically viable. Other major issues include blood-incompatibility [229] and endotoxin contamination [230, 231], with the latter being liable for nearly 30% of the failed preclinical assessments by the US NP Characterization Laboratory [59].

Consequently, alternative means of targeting like TME modulation [232–234], and biological methods like cellular hitchhiking [235], extracellular vesicles [236–238], and even attenuated bacteria [239, 240] are also prominently being considered as potential solutions to the above issue of NC delivery [241].

Cancer Stem Cell Targeting

CSCs are indisputably important to the progression and the severity of cancer; they are consequently very potent as targets for various cancer therapies. However, CSC heterogeneity makes it difficult to associate a cellular marker for a CSC niche. Furthermore, even if a more generic marker like CD44, CD133, or ALDH was to be targeted, these markers are often shared with normal stem cells, negating the primary advantage of high-specificity that is the premise of nanotherapy [56, 242]. Thus, the alternatives are to either target a group of cellular markers or the regulation of stemness pathways, or even a combination of both.

Because CSCs have such a high degree of heterogeneity, targeting an individual cell-surface receptor or marker often proves ineffective. Thus, the characterization of marker combinations specific to certain cancers is an integral part of successful drug targeting. The most universally common markers across the span of different cancers are CD44, CD133, EpCAM, and ALDH [6, 58, 76, 243]. These markers would be beneficial if used in the context of localized treatment; if the treatment is administered directly to the tumor, marker specificity is less of a concern and the emphasis is on therapy intake over accurate delivery. Alternatively, these markers are often used in tandem with another, more specific marker as a means of ensured uptake. The cancer-specific marker is dealt the responsibility of limiting the drug delivery to a specific CSC niche, whereas the more common marker makes sure the drug is without fail taken up by the cell—the more frequent cell markers often deal with metastasis and general cancer progression processes associated with stemness as compared to histology-specific properties, which is why targeting them is a fairly sure-shot means of assured drug administration [15, 21, 22].

While surface markers are an incredibly effective means of targeting CSCs, the degree of influence a treatment possesses depends directly on the efficacy of the drug compound and its successful intake by the cell. The system here works towards simply killing the root cause and doesn't take into consideration the interactome around the tumor cells that is responsible for the progression of the cancer. Given the recently developed role of epigenetics in stem cell differentiation [244, 245], transcription factors like Sox-2 [246, 247], Oct-4 [248, 249], Nanog [92, 250], CXC-R4 [244, 245], survivin (Birc5) [251–253], nestin [254], and Klf-4 [255] and their co-expression [255–258] are also promising avenues through which to capacitate efficacious therapy [91, 259]. When considering CSCs as the point of attack within the TME—wherein targeting CSCs via microenvironment

subsections of hypoxia, vasculature, and cellular components such as TAMs or CAFs is prevalent [67, 260]—a far more potent approach would be to target the stem cell pathways that imbue these cells with the properties of plasticity, heterogeneity, and increased proliferation, which are answerable to ineffective treatment. The pathways most prominently associated with Wnt/β-catenin [89, 261–263], Notch [87, 264, 265], Hedgehog [81, 82, 266], NF-kB [267–269], JAK/STAT [270–274], PI3K/PTEN/AKT [102, 275], and PPAR [276, 277] pathways, all of which, in addition to the properties listed above, display common tendencies towards proliferation, tumorigenesis, metastasis, and survival, as well as secondary stem traits like drug resistance and self-renewal. By extension, the increased frequency of stemness pathways in breast, lung, liver, colon, and rectal cancers is an indicator that CSCs might also be playing a role in cancerous incidence. Statistically, cancers that have a higher degree of involvement from multiple stem cell pathways have an increased chance of emergence, simply because the higher replication rates of stem cells allow for increased mutagenic prevalence [278]. Targeting these pathways, then, is a direct parry on the defense that stem cell involvement provides regular tumor cells against current therapeutic protocols (Table 1).

NC-based regimes have shown high efficacy against these internal and external biomarkers [279, 280] and have considerable potential in this particular application of oncotherapeutics. While combinational therapy in the sense of the loaded agent has been received with widespread applicative popularity, targeting multiple markers is limited by the marker location—as of such, combinational therapy of an internal biomarker and an external one together is yet to receive experimental consideration. Although there is insufficient scientific evidence, multi-level targeting can be argued to be more effective, especially when it comes to attacking CSCs, because it hinders both of their mechanisms of escaping apoptosis (self-renewal and multilineage differentiation) [83], thus improving chances of therapeutic results.

An effective model, hypothetically, would be of an NC that can target CSCs both at the cellular and the genetic levels [140, 281]. As such, this would be possible through means of either a multifunctional ligand or multiple ligands that can be separately functionalized with different stimuli, as depicted within (Fig. 3). In the case of the former, the ligand's conformational changes in response to separate stimuli (ideally of different natures altogether) will enable specificity towards surface and core biomarkers individually. Unfortunately, this will require either the fortuitous discovery of a peptide sequence that is sensitive to a variety of environmental responses—with subsequent conformations compatible to a pair of common CSC biomarkers—or the synthetic design of a similar one. Both cases will require several rounds of design and optimization, entailing that such a ligand will not make an entry into the therapeutic market any time soon. As for the latter design of NCs conjugated with multiple ligands, the potential of immediate application is comparably higher. Both ligands can either be introduced dormant, with two separate stimuli to activate corresponding ligands, or with the ligand specific to the surface biomarker already functionalized. Having one pre-functionalized ligand improves the ease of design on several attributes: ligand sensitivity to the cellular microenvironments can be overlooked if it need not be activated; managing steric hindrance becomes easier as only one of the conjugates will be undergoing conformational changes towards functionality. However, this model must also contemplate how the functionalization of the second ligand will be affected by the conformation of its pre-functionalized companion—including an inspection of potential channels to inactivate or detach the same. While multifunctionalized NCs do show a great deal of promise in theory, effective optimization of ligand density, its effect on protein adsorption, as well as covalent attachment of the therapeutic agents to the functionalized NP for endocytosis and binding selectivity is still underdeveloped, forming an impediment in such NPs' widespread use [282, 283]. Moreover, they also mandate a real-time tracking system to ensure accurate drug disposal, which only further encumbers their realization.

Nanocarrier-Based Cancer Therapeutics

Since its ideation, nanomedicine has consistently been a front runner for the next novel alternative in oncotherapy.

Table 1 High-Frequency CSC Markers for Common Cancer Types

Cancer type	Breast	Colon	Glioma	Lung	Prostate	AML
Markers	$CD44^+/CD24^-$ ALDH1 CD90 α_6-integrin Bcrp-1 IL-2 SDF-1 /CXCR4	$CD133^+$ ESA + CD166 β-catenin LGR5 ABCG5 Survivin $CD44^+$/EpCam	CD15 CD133 α_6-integrin Nestin Sox-2 L1CAM SALL4 OLIG2	ABCG2 ALDH1 CD133 CD90 CD117 CD176	PSA ALDH1 CD44 CD133 α_6-integrin α_2/β_1-integrin	$CD34^+/$ $CD38^-$

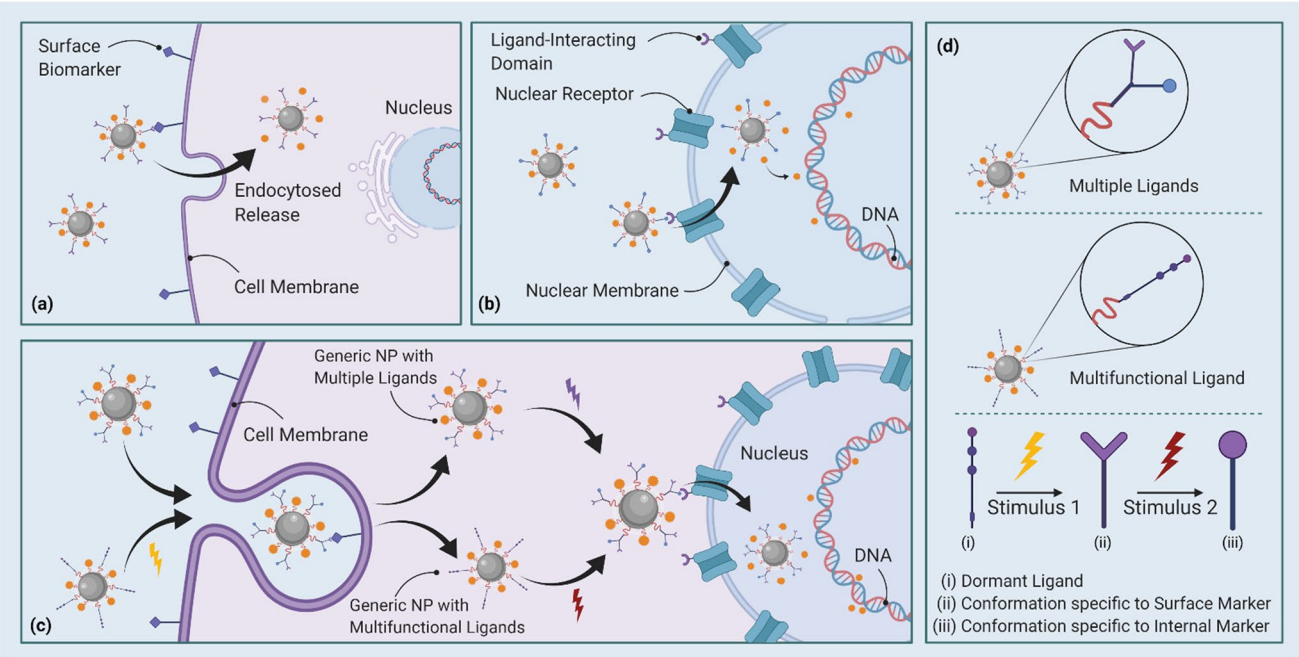

Fig. 3 Model for multi-level targeting of CSCs via multiple or multifunctional ligands. **a** Targeting through surface biomarkers, **b** Targeting through ligand-interacting domain on the nuclear receptor, **c** Targeting through generic NP with multiple and multifunctional ligands, **d** Representation of multiple and multifunctional ligands. The above figure describes the basis through which prevalent NC-mediated targeting of CSCs via surface biomarkers (a), and genetic biomarkers (b), can be hypothetically merged into a model launching a multi-level attack (c). The model involves two ligand-orientation hypotheses, enabled through rounds of varying stimuli (d). The first is of a generic NP conjugated with two or more ligands that are respectively compatible with the external and internal markers being targeted. The functionalization of these ligands is a matter of steric organization and will differ in pertinence to the stem cell niche. The second model is of a multifunctional ligand that can be coaxed into different conformations compatible with specific levels of biomarkers, via rounds of distinct stimuli. (Created with BioRender)

To date, cancer remains the primary genre of NP-based clinical trials at 65%, despite a distinct increase of interest in other areas of application, including anesthesia, inflammation, and infection, over the past decade [21, 33]. NCs have proven extremely versatile in their involvement, even within the umbrella of 'cancer.' Not only do they cater to the severe variation within cancer histology, but they also allow for control on the nature of the therapeutic delivery.

Having concluded that CSCs are the most potent target for cancer-specific nanotherapy, we reviewed several clinical trials and case studies in hopes of narrowing down upon a wide-effect system with specifications for the nature of the NC, the most effective style of delivery as well as the CSC marker. While there are several ongoing and successfully completed clinical trials dealing with the nanoparticular administration of anti-cancer agents [284–295], the specific niche of CSC-targeted NCs remains to be clinically broached. The findings from the review, which consist primarily of pre-clinical in vitro models, have been organized within (Table. 2).

Although there are several studies designed around the involvement of NCs in directed cancer therapy, most choose to target other aspects of the tumor biome over CSCs. The below table collates the most commonly used NCs targeting CSC markers, listing research with efficacies higher than 85%, determined on the basis of comparative CSC growth inhibition.

While NCs can be used in a variety of formats (drug carriers, direct therapeutic agents, passive carriers for antibodies), purely based on frequency, a general representation of the current upcoming nanomedicine regime for CSC therapeutics would be of a drug carrier (most likely a metal or polymeric NP or a liposome) ferrying salinomycin in combination with another anticancer drug [212, 299, 300, 307, 317]. In terms of sheer potency, drugs like paclitaxel and doxorubicin have an upper edge over salinomycin in tumor toxicity, as is explained by their frequent use in chemotherapy. However, their lack of specificity means that their administration runs the risk of several side effects, including myelosuppression, neurotoxicity, cardiovascular toxicity, gastrointestinal reaction, and hair loss [307].

Salinomycin, however, has very high specificity towards CSCs because it targets ABC-binding transporters, as well as the Wnt/β-catenin, Hedgehog, Notch, and Akt signaling pathways—thus ensuring a direct treatment for all the aspects of stemness that hinder cancer treatment [317, 318].

Table 2 Nanocarrier Systems for Various Cancer Stem Cells

Nanocarrier	Therapeutic Agent	Cancer Type	Delivery Model	Cell Line	CSC Marker	Cellular Uptake	Change in Lifespan	CSC Viability
Graphene oxides (GO)	-	Breast	GO flakes in 5% DMSO-distilled water dispersions in local targeting [296]	MCF-7	Wnt/β-catenin, Notch, NRF2, INFγ-STAT1	-	-	40%
	Salinomycin	Ovarian	RPE-rGO-Ag nanocomposite [297]	A-2780	ALDH1, CD133	-	-	15%
Dendrimers	siRNA	Brain	Anti-Lyn siRNA loaded onto phosphorous dendrimer [298]	BTSC-233, JHH-520, NCH-644	CD47, PD-L1, TIM3	80%	-	25%
Carbon nanotubes (CNT)	Salinomycin	Gastric	Chitosan-coated SWCNT activated by hyaluronic acid (SAL-SWCNT-CHI-HA) [299]	AGS	$CD44^+$	21%	+30 d	11%
	Paclitaxel, Salinomycin	Breast	CD44 antibody hydrazone-linked onto SWCNT with pH activated release system [300]	MDA-MB-231	$CD44^+$	50%	-	25%
Gold sphere nanoparticles (Au-NP)	siRNA	Breast	Au-NP conjugated with multiple units of glucose-polyion complexes linked with lipoic acid (Glu-PEG-PLL-LA) [301]	MDA-MB-231	GLUT1	35%	-	50%
	Salinomycin	Breast	PEGylated Au-NP (SH-PEG-NH_3) [302]	MCF-7	$CD24^-$, $CD44^+$	63%	-	25%
	CD44v6 mAB	Gastric	PEGylated Au-NS conjugated with CD44v6 monoclonal antibody [303]	MKN-45	CD44	83% (non-specific)	+28 d	89.2%
	Teleglenastat	Brain	PEGylated Au-NP conjugated with CD133 aptamers loaded with teleglenastat (Au-PEG-CD133-CB-839) [304]	GBM-1, NCH-644	CD133	30%	-	50%
Gold nanorods (Au-NR)	Adriamycin	Liver	EpCAM antibody conjugated onto lipophilic Au-NR [305]	Hepa 1–6	EpCAM	27%	-	20%
	CXCR4 antibody	Gastric	Au-NRs conjugated with CXCR2 antibody (AuNR-SiO_2-CXCR4) [306]	MGC-803	SDF1	75%	+21 d	40%

Table 2 (continued)

Nanocarrier	Therapeutic Agent	Cancer Type	Delivery Model	Cell Line	CSC Marker	Cellular Uptake	Change in Lifespan	CSC Viability
Liposomes	Paclitaxel, Salinomycin	Lung	AEYLR peptide-PEG-modified paclitaxel loaded nano-structured lipid carrier (NLC) [307]	NCI-H1299	CD133	95%	-	31.4%
	Docetaxel, Telmisartan (pre-treatment)	Lung	Docetaxel loaded PEGylated liposomes [308]	NCI-H460	CD133	96.4%	-	20%
	Curcumin-difluorinated (CDF)	Head and Neck	Liposomal CDF suspended in 0.9% NaCl, injected intravenously [242]	CCL-23R, UM-SCC-1R	CD44	-	-	45%
	Doxorubicin, Salinomycin	Liver	Redox-triggered dual-targeted liposome [309]	Huh-7	CD133, EpCAM, (Sox-2, Oct-4)	86%	-	11.8%
Polymeric nanoparticles (PNP)	Doxorubicin, Thioridazine	Breast	Both compounds loaded onto separate MTC-OBn polymer-ring micelles and delivered in-tandem [310]	BT-474, MCF-7	$CD24^{-}$, $CD44^{+}$	40%, 54%	-	20%
	Salinomycin, Docetaxel	Gastric	Both compounds loaded onto separate poly(D,L-LA-co-glycolic acid)-PEG PNPs but delivered in-tandem [311]	MKN-45, HMNI-N87	$CD44^{+}$	80%	-	40%
	siRNA	Brain	PEG-PLA PNP loaded with FAM-siRNA [312]	U-251, U-87MG	GLUT3	60%	-	48%
	Naproxen	Breast	PNP coated with hyaluronic acid (HA-NP) [313]	MCF-7	$CD44^{+}$, Cox	65%	-	45%
	miR-486	Lung	Cationic lipid core-crosslinked NPs (CCL-486) [314]	NCI-H460, NCI-A549, NCI-H1299	CD133, PI3K/AKT	78%	-	12.5%
	Paclitaxel	Lung	PGLA-PEG PNPs conjugated with CD133 aptamers [315]	HCC-827, A-549, A-431	ALDH, CD133	80%	-	40%
	Curcumin, Salinomycin	Breast	PEGylated PNPs conjugated with hyaluronic acid (HA-PEG-PLGA-Cur-Sal) [316]	MCF-7	$CD24^{-}$, $CD44^{+}$	96%	-	10%

It also activates the p38 MAPK cascade which helps induce ROS-mediated apoptosis [319, 320]. Any combinational therapy with salinomycin consequently proves incredibly effective when it comes to CSC-specific therapy, as has been proven with in vitro trials. For instance, smart liposome-based systems co-delivering doxorubicin and salinomycin were found effective in reducing stemness in liver CSCs [309] whereas a combination of salinomycin and docetaxel loaded onto PNPs proved a promising strategy when targeting gastric CSCs [311]. Besides co-delivery systems, preclinical studies also show salinomycin derivates as capable of targeting CSCs successfully on their own, although predominantly within breast cancers models [321–323].

Despite its many promising properties in CSC targeting, administering salinomycin does come with certain obstacles—particularly in its aggressive hydrophilicity [318, 324]. This entails a dependency on nanodelivery, which can hinder its long-term relevance as issues of toxicity and systemic flushing continue to stand in the way of NC-based therapeutic systems circulating the market [26, 325]. Functional changes like conjugation with PEG or Vitamin E to form a prodrug can improve its solubility, but the design's efficacy is acceptable only when employed within an NC-based format [324, 326, 327].

While not heavily scrutinized in this review, exosomes do present a promising alternative for NCs as they have already been characterized to be heavily involved in the crosstalk between CSCs and the TME and thus do not need to be additionally functionalized for specificity, and can also overcome biocompatibility issues that other inorganic DDSs are hindered by [279, 328–330].

It is also of notable import that a major portion of the current clinical trials that target CSCs are directed towards either breast or other solid tumor cancers. Despite there being no definitive proof hinting that nanotherapy has reduced effects on other cell types, the above trend can be used to hypothesize that NCs can target endothelial cells to a higher degree than other cell histologies [331].

As has been discussed, CSCs can be targeted via the two avenues of cellular markers or stemness pathways. Aside from delivering anticancer drugs, NCs can also be employed in a parallel system as vehicles for immunotherapy [332]. When considering cell surface markers, commonly used therapeutic agents include surface antigens (SAs) and immune checkpoint blockades (ICBs); alternatively, the aspects of immunotherapy engaged in pathway interactions include inhibitors for Wnt, Notch, Hedgehog, PI3K, and other metabolism or niche mechanisms [90, 265, 333]. While the focus of this paper is on the optimization of current NC-based systems in targeting stem cell markers and pathways, alternative CSC applications like CSCs as vehicles of delivery [238, 334, 335] or even infused stem therapy [336] cannot be dismissed. As such, MSCs in the context of therapeutic carriers are gaining rapid popularity as a strategy to ensure ameliorated side-effects on account of improved biocompatibility [332, 337].

Conclusion

TMEs are a crucial aspect of cancer progression and play major roles in tumorigenesis, metastasis, and even relapse. Because they interact with almost all aspects of the tumor biome, TMEs can often be too large to successfully silence simply by blocking or competing against some of its constituent cells. In remediation however, CSCs prove to be ideal focal points for TME-directed targeting on account of their central role within TMEs. Common CSC markers across various niches include CD133, ALDH-1, CD44, and CD24, although there are several CSRs that are more niche-specific and thus better for drug delivery targeting. Furthermore, targeting common markers present significant limitations given the fact that they do not deliver in their promise of identifying all CSCs. Because stem cell populations amplify tendencies towards clonogenic and tumor heterogenic processes, common markers most often can't recognize more than specific cell subpopulations. Moreover, they're often also expressed on normal stem cell surfaces, which only reduces the efficiency of the targeting system. Thus, as a general modicum, common CSC markers are often used in combinational targeting, whereas more specific markers are focused upon for stand-alone targeting mechanisms.

While targeting systems have consistently been with CSRs in mind, if they are implemented toward stem cell pathways, they would be arguably more effective and even potentially overcome issues of MDR and relapse. There is a definitive turn in targeting systems toward stemness, but because common stem cell pathways like Wnt, Notch, and Hedgehog are also heavily involved in regular cell proliferation and maintenance systems, contained impairment of the pathway in a manner that doesn't bleed the effects onto neighboring cell biomes is yet to be conclusively defined. This is partly because much about the TME is yet to be uncovered. While there have been decisive leaps in the characterizations of several cellular and non-cellular components within microenvironments, their functions or signaling mechanisms are yet to be entirely chalked out. So far, the focus has been on major stromal and immune cell types and specific cell populations indigenous to particular stem niches. However, TME–CSC crosstalk in a physiologic context remains understudied. Pre-established organoid approaches towards cellular crosstalk have definitely improved in vitro modeling, but understanding at a microenvironment level of bio-nanointerfaces is essential for the further establishment of nanoparticular delivery systems.

Currently, organic NCs like liposomes or PNPs are particularly selected for, especially for more challenging target locations like brain tumors on account of higher biocompatibility. But as a whole, metallic NPs and carbon-based NPs are gaining wide-range popularity as mediums for drug targeting as well. The defining factor remains in how non-organic NPs need to undergo surface functionalization to mimic biocompatibility that their organic counterparts forego. Current protocol leans towards focused administration of pre-existing chemotherapeutics, perhaps in facilitation of response to disease urgency than for lack of scientific novelty. While this methodology has been producing steady results with improved drug efficacy and higher rates of recovery, it remains a fact that the current line of NC-based targeting systems isn't efficient enough to entirely keep highly toxic compounds like doxorubicin, paclitaxel, docetaxel, and temozolomide from leaking into the surrounding microenvironment. Aside from synthesizing a new drug altogether, an alternative could be to turn towards a different range of drugs, especially if the point is to target stemness. While salinomycin has become a commonly employed compound in such contexts for its stem-specific targeting, other polyether antibiotics can also be considered for similar applications.

As such, there is significant advancement in the delivery aspect of drug administration. Nonetheless, with the establishment of better targeting machinations comes the need for ponderings on some other important aspects, including methods to monitor NC accumulation within the system, the requirement for a toxicity standard, and even the shift of current targeted delivery towards individualized therapy. These are only some of the questions that incoming research can aim to elucidate upon.

Abbreviations ABC: ATP-Binding Cassette; AIE: Aggregation-Induced Emission; Au-NP: Gold Nanoparticle; Au-NR: Gold Nanorods; BBB: Blood-Brain Barrier; CAF: Cancer-Associated Fibroblast; CNS: Central Nervous System; CNT: Carbon Nanotube; CSC: Cancer Stem Cell; CSR: Cell-Surface Receptor; CTC: Circulating Tumor Cell; DC: Dendritic Cell; DDS: Drug Delivery System; ECM: Extracellular Matrix; EGF: Epidermal Growth Factor; EPR: Enhanced Permeability and Retention; FGF: Fibroblast Growth Factor; GO: Graphene Oxide; HGF: Hepatocyte Growth Factor; HK: Hexokinase; iPSC: Induced Pluripotent Stem Cell; ICAM: Intercellular Adhesion Molecule; ICB: Immune Checkpoint Blockade; MDSC: Myeloid-Derived Suppressor Cell; MPS: Mononuclear Phagocytic System; MSC: Mesenchymal Stem Cell; NC: Nanocarrier; NEC: Neuroendocrine Cell; NP: Nanoparticle; PDGF: Platelet-Derived Growth Factor; PNP: Polymeric Nanoparticle; TAA: Tumor-Associated Antigen; TAM: Tumor-Associated Macrophages; TEC: Tumor-Associated Endothelial Cell; TGF: Transformation Growth Factor; TIL: Tumor-Infiltrating Lymphocyte; TME: Tumor Microenvironment; VEGF: Vascular Endothelial Growth Factor

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Declarations

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