A new prospect in cancer therapy: targeting cancer stem cells to eradicate cancer

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Abstract

According to the cancer stem cell theory, cancers can be initiated by cancer stem cells. This makes cancer stem cells prime targets for therapeutic intervention. Eradicating cancer stem cells by efficient targeting agents may have the potential to cure cancer. In this review, we summarize recent breakthroughs that have improved our understanding of cancer stem cells, and we discuss the therapeutic strategy of targeting cancer stem cells, a promising future direction for cancer stem cell research.

Key words Cancer stem cells, targeting therapy, pharmaceutical carriers

Advances in medical investigation have fostered a deeper understanding of cancer, from tissue anatomy to molecular mechanisms of tumor initiation and development. However, there is no consensus on how cancers are initiated or how they develop from small neoplasms to fatal tumors. Based on experimental evidence, scientists have proposed that tumors may possess cells similar in phenotype to normal stem cells and that these cancer stem cells (CSCs) are the origin of tumors.

At the end of the 20th century, Canadian scientists identified a hierarchy in leukemia cells, a breakthrough that laid the foundation for CSC research and cast new light on cancer therapy. Here, we will summarize recent discoveries about CSCs and discuss how the cancer stem cell theory has impacted the potential for targeted therapy.

Cancer Stem Cells and Cancer Stem Cell Theory

The cancer stem cell theory, which suggests that CSCs are the origin of cancers, can be explained by models of tumor initiation: the stochastic model, the hierarchy model, and the clonal evolution model. In the stochastic model, tumors are described as homogeneous tissues. When activated by intrinsic or extrinsic factors, some cells with the ability to initiate tumors may have stem-like phenotypes. It means that tumors can be initiated by any one of the remaining stem-like cells after conventional therapy.

On the contrary, some scientists posed hierarchy model, tumors and normal tissues possess a similar hierarchy, consisting of both stem-like cells and highly differentiated cells. The clonal evolution model is similar to the stochastic model or the combination of the stochastic and hierarchy models. Both models infer that tumors may be initiated by some certain cells, which were termed as stem-like cells. Many evidences occurred to support the hypothesis.

In fact, researchers have started the study of CSCs in the early 20th century. During the long period of investigation, numerous experiments have been performed and have provided proofs of CSC occurrence.

Brief history of cancer stem cells

Bomken et al., citing the 1937 landmark article by Furth and Kahn, stated that about 5% of leukemia cells could be transplanted successfully through a series of experiments in which leukemia cells were inoculated into inbred mice. Studies on solid tumors, such as transplantation experiments with Yoshida sarcoma, produced analogous results, verifying that some tumor
Cancer stem cells and targeting therapy

Significant experimental evidence supports the hypothesis that most tumors are heterogeneous tissues. In 1997, Bonnet et al.\(^6\) demonstrated that leukemia cells are a heterogeneous population and found that CD34\(^+\)CD38\(^-\) leukemia cells could act as hematopoietic stem cells to initiate acute myeloid leukemia (AML) in inoculants. Thus, CD34\(^+\)CD38\(^-\) cells were deemed CSCs in leukemia.

Subsequently, researchers identified and isolated CSCs from many different cancers. These include most hematopoietic cancers, such as AML\(^1,2,4\), acute lymphoid leukemia (ALL)\(^3\), and chronic myeloid leukemia (CML)\(^7\), as well as solid tumors. In solid tumors, CSCs were identified by specific biomarkers, such as CD133\(^+\) for...
CSCs in glioblastoma multiforme (GBM)\textsuperscript{[7,9]} and CD44\textsuperscript{+} for CSCs in breast cancer\textsuperscript{[1,7,8]}. CSCs have also been found in pancreatic cancer\textsuperscript{[8,9]}, head and neck cancer\textsuperscript{[8]}, lung cancer\textsuperscript{[10]}, bladder cancer\textsuperscript{[11]}, prostate cancer\textsuperscript{[12]}, gastric cancer\textsuperscript{[13]}, melanoma\textsuperscript{[14]}, and hepatocellular carcinoma\textsuperscript{[15]}. Thus, CSCs have been hot topics in cancer research and targeted therapy.

**Characteristics of cancer stem cells**

Cancer stem cells, as the name implies, refer to a subpopulation of cancer cells similar to human normal stem cells\textsuperscript{[11,7]} that have the capacity for self-renewal, differentiation into multiple cancer cell lineages, and extensive proliferation\textsuperscript{[7,10,16]}. In spite of notable progress made in recent years, there is currently no definite information about the origin of CSCs. According to the origins, CSCs may initiate tumors with distinguished malignancy levels. Stem cells in normal tissues, malignantly transformed progenitor cells, or even terminally differentiated cells may form CSCs\textsuperscript{[7,9]}. Other research indicated that cancer type is closely associated with the origin of the tumor. During the process of differentiation, malignancy may happen at any point. The lower the degree of CSC differentiation is, the more malignant the tumor initiated by CSCs will be\textsuperscript{[7]}

Owing to their proliferation potential, CSCs are widely accepted as one source of cancer recurrence after conventional therapy. Further, because of their potency in inducing tumorigenesis, CSCs are purported to contribute to tumor initiation. According to studies undertaken over the years, five characteristics of CSCs have been identified\textsuperscript{[7,10,16]}: (1) CSCs can initiate new tumors, and this requires only a small amount of CSCs; (2) CSCs possess specific and distinguishing markers by which they can be isolated; (3) CSCs can differentiate and self-renew; (4) CSCs can be transplanted one generation after another; and (5) CSCs tend to be resistant to conventional therapies including conventional chemotherapy and radiotherapy\textsuperscript{[9]}, and failure to eliminate CSCs with these therapies may cause recurrence. Furthermore, CSCs may promote angiogenesis during tumor development in some cancers such as glioma\textsuperscript{[8]}. Given these characteristics, one can infer from cancer stem cell theory that it is impossible to cure cancer without eliminating all CSCs. Therefore, the biggest barrier in cancer therapy lies in determining how to precisely target and eliminate CSCs.

Notably, some studies suggest that cancer stem cell theory may not explain all cancer initiation. For instance, researchers have not isolated CSCs from B-cell precursor ALL\textsuperscript{[10]}. Thus, the question remains whether this simple model can mimic all tumor initiation. Studies of cancer initiation and development, therefore, remain crucial.

### Specific markers of cancer stem cells

Gupta et al.\textsuperscript{[19]} summarized three properties exhibited by CSCs in vitro: (1) CSCs can be isolated by distinctive surface markers; (2) CSCs can form tumor spheres in suspension culture; and (3) CSCs are much more chemoresistant and invasive than other tumor cells. Currently, there are several methods to specifically isolate CSCs in vitro. These include specific marker\textsuperscript{[1,9,10]} or Hoechst staining-based isolation\textsuperscript{[20,22]}, chemoresistance-based isolation\textsuperscript{[24]}, heterogeneity of invasiveness sorting\textsuperscript{[25]}, and, in metastatic breast cancer cells, reoxygenation sorting after exposure to repetitive cycles of hypoxia\textsuperscript{[26]}. Marker and Hoechst staining-based isolation are widely used approaches.

CSC markers are membrane proteins specifically expressed on the surface of CSCs, including, for instance, receptors and antigens. CSC surface markers vary by tumor type (Table 1). Thus, one goal of CSC research is to discover specifically expressed surface biomarkers for different tumor types. With this knowledge, tumor types could be distinguished by relevant biomarker antibodies, and screening experiments could be conducted with flow cytometry.

Many CSC surface markers have been discovered, but their specificity remains unconfirmed, as some of the markers have also been found on the surface of normal stem cells or even normal differentiated cells. In fact, some markers considered as CSC-specific are not sensitive enough to screen CSCs from large numbers of tumor cells. For example, CD133, a glycoprotein found in humans and rodents, was regarded as a candidate marker for CSCs. However, studies in GBM cell lines and primary tumor tissues indicated that both CD133\textsuperscript{+} and CD133\textsuperscript{-} GBM tumor cells were oncogenic\textsuperscript{[26,27]}, revealing the uncertainty of the surface markers. Hence, finding specific markers is a high priority in CSC therapy research.

### Tracing and Targeting Cancer Stem Cells In Vivo

For exploring new options of cancer therapy, in vitro experiments cannot replace in vivo research. However, tracing the location of CSCs and monitoring their physiologic indexes in real-time is difficult in vivo. Therefore, developing techniques that can be applied to study CSCs in vivo will have an important impact on clinical diagnosis and therapy for cancer. CSC tracers must be well designed. The particularity of the internal physiologic environment, such as the homeostatic state, pH and enzyme activity, sets high demands for tracer biocompatibility. Moreover, tracers should not perturb the physiologic activity in experimental animals or produce toxic or side effects. Finally, when tracers are introduced
paramagnetic iron oxide nanoparticles (SPIONs) have tactics. Mesenchymal stem cells marked with super-effective magnetic contrast medium and potent locating biocompatible shells for the nanomaterials. To cells, suggesting the need to identify nontoxic and biocompatible shells for these nanomaterials. Magnetic resonance imaging (MRI) requires effective magnetic contrast medium and potent locating tactics. Mesenchymal stem cells marked with superparamagnetic iron oxide nanoparticles (SPIONs) have been applied in MRI. Researchers injected SPION-labeled mesenchymal stem cells into rats and then directed the particles to a desired site using a magnetic field. Lewin et al. linked Tat peptide, an amino acid sequence from HIV-1 that mediates protein internalization, to the surface of superparamagnetic nanoparticles, and then carried out a tracing investigation by MRI. Since Tat peptide–labeled nanoparticles can be effectively internalized by hematopoietic stem cells and neural progenitor cells, they can localize to hematopoietic and neural tissues and cells. Lee et al. detected human epithelial cancer by using MRI to trace antibody-conjugated multifunctional magnetic gold nanocomposites (MGNCs) and performed localized synchronous therapy. Thus, after altering antibodies to specifically target CSCs and refining the method, these nanoparticles could potentially be applied to trace CSCs in vivo.

Strategies for targeting cancer stem cells in vivo

To a great extent, successful tracing depends on effective CSC targeting techniques. At present, CSC targeting is primarily accomplished with antibodies and is directed to CSC-specific surface markers, CSC-specific signaling pathway components, and CSC niches. Targeting CSCs via CSC-specific surface markers is the commonly used technique. Surface marker CD44 was used as a target in AML therapy. Similarly, anti-CD44 antibodies H90 and A3D8 were used to promote the differentiation of AML CSCs, thereby inhibiting proliferation and accelerating apoptosis. Additional studies on targeting drug resistance proteins and other cancer-relevant antigens are being undertaken. Currently, there are no widely acknowledged markers specific to CSCs for any tumor type. Indeed, many of the known markers also exist on the surface of normal cells, which

Table 1. Surface markers and phenotypes of different cancer stem cells

| Tumor type         | Cell surface biomarker and phenotype |
|--------------------|--------------------------------------|
| Acute myeloid leukemia | CD34+/CD38- [1,5,14] |
| Acute lymphoid leukemia | CD34+/CD19- [17], interleukin-3-receptor α, CD33 [17] |
| Breast cancer      | CD44+/CD24+/ESA+/CD133+/lin/ADH+/CD44+/CD24+/ESA+ [17,18], SSEA-1 [17] |
| Glioblastoma multiforme | CD133+/CD44+/ESA+ [19,20], CD166+/CD26 [21] |
| Colorectal cancer  | CD133+/ESA+/CD44+/CD26 [22] |
| Pancreatic cancer  | CD133+/CD44+/ESA+ [5,12], CD133+ [5,12] |
| Prostate cancer    | CD44+/CD133+/CD26 [23], CD44+ [10] |
| Lung cancer        | Sca+/CD45+/Pecam+/CD34+ (lung adenocarcinoma) [24], ALDH+/Oct4+/CD34+/ABCG2+/CXCR4+ [25] |
| Liver cancer       | CD133+/CD44+/CD26+ [26], EpCAM+/AFP+ [26] |
| Bladder cancer     | EMA+/CD44+ [27] |
| Gastric cancer     | CD133+/CD44+ (primary tumor), CD44+/CD133+/CD44+/ALDH1 (+) [28] (metastasis) |

in a clinical setting, giving a patient relief from pain should be considered as well.

Strategies for tracing cancer stem cells in vivo

Two main strategies are used to trace CSCs in vivo: labeling tracing and magnetic resonance imaging (MRI).

For labeling tracing, probes, namely fluorescent proteins like green fluorescent protein (GFP) and small molecules, are widely used. Studies showed that low activity of 26S proteasomes could promote tumorigenicity by stimulating stem-like properties in cells [29,30], and 26S proteasomes have been set as tumor therapy target [31]. In light of these discoveries, Vlashi et al. used ZsGreen fusion protein as probe to target cells with low 26S activity, thereby indirectly targeting or tracing CSCs. Some dyes such as biarsenical can be excited to emit fluorescence, and could be used in tracing CSCs when covalently linked with specific targeting amino acid sequences [32]. Hence, the dyes can be used to sort cells with specific surface markers by detecting a fluorescence signal. Because nanomaterials are small scale and have special properties, they are becoming more common in cell tracing applications. Among the variety of nanomaterials available, quantum dot tracing agents are currently under wide investigation. Nanocrystals, one type of quantum dot, have good solubility in buffers and fine photoluminescence properties [33], making them excellent prospects for tracing cell structures and living cells. Nevertheless, a majority of quantum dots are toxic to cells, suggesting the need to identify nontoxic and biocompatible shells for these nanomaterials.
poses a challenge for clinical translation of this potential therapeutic strategy. CSC targeting approaches using non-specific markers may aberrantly affect normal tissues and result in toxic side effects. Hence, to advance the potential for targeting CSCs through surface makers, new studies to identify CSC-specific surface markers are needed in the future.

Many studies show that CSCs do not share the same signaling pathways as normal cells, especially normal stem cells. Because abnormalities in signaling pathways may lead to malignant transformation, targeting specific components in CSC signaling pathways is another strategy in CSC-targeted therapy. Wang et al.\(^{(40)}\) found that aberrations in the Wnt/β-catenin pathway are likely to induce hematopoietic stem cell transformation into leukemia stem cells, which are purported to cause AML. Vilimas et al.\(^{(41)}\) reported that overactivation of NF-κB in T-cell ALL may lead to malignant transformation of hematopoietic stem cells; thus, targeting NF-κB and inhibiting its activity could be a prospective target in T-cell ALL therapy.

Cells in vivo need to interact with their surrounding microenvironment. Cell-intrinsic and cell-extrinsic factors distributing around the microenvironment regulate cells physiologic activities. Normal stem cells also need the factors to maintain their stem-like features and homeostasis. This suggests that there must be a balance between differentiated and undifferentiated cells in the stem cell population. The microenvironment helps to maintain stem properties by providing essential factors such as Notch, Wnt, and bone morphogenetic protein (BMP). For example, when the Notch pathway is activated, the effector protein hypoxia-inducible factor-1α (HIF-1α) induces retention of glioblastoma stem cell features by maintaining hypoxia\(^{(42)}\).

Many factors distributing around the microenvironment are signaling pathway-related components. CSC niches are similar to normal stem cell niches, but some specific signaling pathways are dysregulated, which leads in distinguished microenvironment in tumor tissues. Some stem cell signaling pathways have been shown to be dysregulated in CSCs. For example, Steg et al.\(^{(43)}\) found that endoglin, a type I membrane glycoprotein that is located on cell surface and is part of the TGF-β receptor complex, overexpresses in tumor cells and presents CSC characteristics to promote the tumor cell survival, chemoresistance, and recurrence in ovarian cancer. In glioblastoma, the U373MG and GBM578 cells isolated from tumor-bearing mice after radiation treatment were considered stem-like cells and were analyzed to activate the Wnt pathway by quantitative real-time reverse transcription–polymerase chain reaction\(^{(44)}\).

In each stage of tumor progression, various components in the environment are needed to support the growth of tumors. Since CSCs have potent tumorigenicity, inhibiting CSC invasion to inhibit cancer relapse and metastasis is a potential therapeutic strategy. Leukemia cells such as ALL cells express C-X-C chemokine receptor type 4 (CXCR4), which has been reported to induce migration of tumor cells to the niches that maintain stem cell properties\(^{(45)}\). Thus, targeting CXCR4 has the potential to destroy the CSC microenvironment.

Many normal stem cells express high levels of ABC transporters\(^{(46)}\). Since CSCs are special stem cells and are reported to be highly resistant to anti-cancer drugs\(^{(47)}\), ABC transporters, which play a critical role in drug resistance, are suggested to regulate the growth of CSCs\(^{(46-48)}\). In fact, researchers observed that several ABC transporters, namely ABCA2, ABCG2, ABCB1/MDR1, and multidrug resistance protein 1 (MRP1), were up-regulated in the side population of human lung cancer cell lines\(^{(21)}\). In addition, retinoblastoma cells, liver cancer cells, and pancreatic cancer cells are reported to have high levels of ABCG2\(^{(48)}\). Therefore, ABC transporters have potential to be antitumor targets\(^{(49)}\).

Furthermore, some CSCs, such as glioblastoma CD133+ stem-like cells\(^{(46,50)}\) or high DNA repair capacity, which keeps cells alive and promotes rapid growth. CSCs can also evade the immune system because of their reduced immuno-genicity\(^{(51)}\). Thus, despite our growing understanding of CSCs, there is still a long way to go in efficiently and accurately targeting these cells.

**Cancer Stem Cell-targeted Therapy and the Development of Drug Carriers**

There are three main strategies for conventional cancer therapy: surgical resection, chemotherapy, and radiotherapy. Surgical resection is still the most potent means to treat certain tumors. However, it has notable limitations: resection cannot cure metastatic cancer completely, and it does not work in hematopoietic cancer therapy. Resection may also influence physical function since excision may remove some normal tissues, causing sequelae. CSCs are known to be resistant to chemotherapy and radiotherapy. Failure to completely eliminate CSCs with these approaches leads to disease recurrence. Cancer stem cell theory has created a new prospect for cancer therapy: targeting CSCs. Therefore, CSC-targeted therapy should be an important part of cancer therapy.

**Strategies for cancer stem cell therapy**

To date, only four CSC-targeted approaches have been used for cancer therapy. These include increasing
Because CSCs can initiate tumors, failure to eliminate them will result in tumor recurrence. Thus, increasing the sensitivity of CSCs to conventional drugs and radiotherapy is a valid approach to eradicate CSCs and prevent tumor recurrence. CSCs also have properties similar to normal stem cells, including insensitivity to conventional chemotherapy and radiotherapy, making them difficult to eliminate completely. Therefore, increasing sensitivity of CSCs to conventional therapy is crucial for improving therapeutic effects[27]. In recent years, study of CSC-specific surface markers, characteristics, signaling pathways, and niches provided evidence at the gene and protein levels to support the theory of CSC-targeted therapy. Strategies such as RNA interference-mediated down-regulation of gene expression, including anti-apoptotic genes, make CSC eradication possible in the future. For example, inhibition of checkpoint kinase 1 (Chk1) and checkpoint kinase 2 (Chk2) activity decreased the resistance of GBM to radiotherapy[9]. L1 cell adhesion molecule (L1CAM) shRNA induced elimination of CD133+ glioma cells, but it had no effect on CD133- cells. Furthermore, some studies report the use of oncolytic adenoviruses to kill CD44+CD24-low breast carcinoma cells[10].

Promoting CSC differentiation is another approach to cancer therapy. Malignant cancer cells are generally derived from poorly differentiated cells, which make them highly tumorigenic. As for CSCs, their self-renewal and differentiation properties make them even more tumorigenic. Inducing differentiation into weakly tumorigenic cells could thus raise the potential for CSC eradication and thereby reduce the probability of recurrence after conventional therapy. Tang et al.[18] was the first to report that BMP could prompt differentiation and reduce the frequency of CD133+ cells. Pham et al.[85] tried knocking down the expression of CD44 in breast CSCs and successfully induced the differentiation of CSCs to non-CSCs.

Other strategies have also been designed based on the properties of CSCs. ABC transporters are up-regulated in many types of tumor cells[21,46], resulting in reduced drug toxicity as well as chemoresistance. Thus, targeting ABC transporters can relieve chemoresistance. As we know, down-regulating the expression or the activities of ABC transporters can inhibit the drug efflux, which benefits to whole tumor cell eradication, including CSCs. Despite the marked advantages of targeting ABC transporters in CSC therapy, some researchers caution that application of ABC transporter inhibitors should be carefully standardized to avoid side effects. Indeed, normal stem cells will also be impacted by inhibiting drug transporters, especially ABCB1/MDR1 and ABCG2, both of which are important in maintaining normal activities in the blood-brain barrier[54].

Strategies for targeting and silencing CSC-related genes to inhibit their growth and self-renewal ability have been investigated in cervical cancer stem-like cells[59]. Blocking the functionally relevant CSC signaling pathway components, such as Akt and signal transducer and activator of transcription-3 (STAT-3) in glioma, is also a recommended approach[58].

 Destruction of CSC-dependent stem cell niches could be a new way to eradicate CSCs. In CSC niches, signaling pathways initiate and facilitate tumor formation[82], and components in the microenvironment protect CSCs against chemotherapy and radiotherapy. A study showed that medulloblastoma CSCs tended to locate around vessels, which reduced the effect of radiotherapy[58]. Hence, there is an urgent need to develop an efficient CSC niche-targeting strategy. The extracellular matrix and soluble factors in CSC niches may be potent targets for therapy. Studies with mouse models showed that vascular endothelial growth factor receptor 2 (VEGFR2) antibodies combined with chemotherapeutic agents effectively reduced the population of CSCs[57]. This suggests that a multifocal strategy involving anti-CSC niche and anti-angiogenesis therapy may have potential for treating cancer.

Moreover, some natural extracts are purported to target CSCs. Luk et al.[86] reported that γ-tocotrienol can reduce the expression level of CSC surface markers on prostate tumor cells. This research group also found that polysaccharopeptide (PSP) extracted from the turkey tail mushroom Coriolus versicolor (also known as Yun Zhi) can target CSCs in prostate cancer[58]. The discovery and application of natural extracts targeting CSCs may open a new door for CSC targeting in cancer therapy research.

**Development of cancer stem cell-targeted nano-drug carriers**

Most anti-cancer agents cannot target cancer cells actively. Furthermore, commonly used anti-cancer agents are toxic to all kinds of cells, causing side effects in normal tissues when homogeneously distributed in the circulation system. Thus, choosing a proper carrier for anti-cancer agent loading and transport to the lesion site can decrease the toxic side effects and produce better therapeutic effects. The development of nanotechnology has created novel opportunities for drug carrier research. Nanomaterials consist of nanoscale elementary units, which possess special properties. Nanomaterial, especially the composites assembled by nanoscale units, have many advantages in loading drugs, including high
drug load content, favorable drug metabolism control when the surface of the material is modified, good distribution and controlled release[60]. Furthermore, some are biodegradable and biocompatible, and some can target specific organs, organelles, or tissues. Nano-materials commonly applied in drug delivery include nanoparticles, e.g., inorganic nanoparticles, polymeric nanoparticles, or liposomes; nanotubes, e.g., carbon nanotubes and quantum dots[60,61]. Each has particular characteristics and drug-loading capabilities. Combining nanomaterials with antibodies against CSC-specific markers or CSC-targeting agents may be a useful strategy in CSC-targeting therapy.

There have been in-depth studies on nanoparticle applications. Gold nanoparticles (AuNPs) are the most commonly used inorganic nanoparticles and tend to be used in bioimaging because they can enter cells easily, present distinct colors in different conditions, and be rapidly detected. When modified in various ways, AuNPs can achieve distinguished tasks in therapy. For example, polyethylenimine (PEI)-modified AuNPs can transfect monkey kidney COS-7 cells better than PEI alone; methoxy-PEG-thiol- or coumarin-PEG-thiol-modified AuNPs will locate mainly in the cytoplasm, perinuclear region[63], and CTAB-coated AuNPs conjugated with peptide can selectively accumulate in the mitochondria of cancer cells[63]. When assembled with other materials to form a composite, AuNPs have potential to be applied in synchronous hyperthermal therapy[62]. When conjugated with CSC-specific antibody or targeting molecules, AuNPs have a potential application in CSC-targeting therapy. Silver nanoparticles (AgNPs) are reported to have antibacterial activities and to induce cytotoxicity and genetoxicity in human cells. AshaRani et al. [64] reported that human glioma cell line U251 is sensitive to AgNPs. Many studies have been undertaken to analyze the drug-carrying potential of inorganic nanoparticles in targeting cancer cells, but their CSC-targeting therapeutic prospects should be rigorously detected before applying drug-loading.

Other inorganic nanomaterials proposed to be appropriate carriers, like carbon nanoparticles, have been investigated. Functional graphite oxide[66] and carbon nanotubes[66] conjugated with targeting molecules like CD133 monoclonal antibody is one prospective construct for CSC-targeting therapy.

Synthesized polymeric nanoparticles have good biodegradation and biocompatibility, and their low antigenicity reduces phagocytosis by the reticuloendothelium[65,67]. Furthermore, their surfaces can be easily modified. By controlling nanoparticle size, target and distribution effects can be changed conveniently to reach an optimal therapeutically efficacious drug carrier systems, such as with polyethylene glycol (PEG) nanoparticles[60].

Increasing amount of nanomaterials have been analyzed about their application potentials in CSC therapy, but merely a small amount of them can be approved to apply to clinical treatment such as PEG carriers. However, the notable advantages of nanomaterials, such as high drug load content, metabolism control, and controlled release, make nano-drug carriers great application prospect in cancer and CSC therapy in the future.

Conclusions

Since the cancer stem cell theory was established, controversies about the existence of CSCs have not ceased. However, cancer stem cell theory does provide a new prospect in cancer therapy. Since CSCs contribute to cancer initiation and recurrence after conventional therapy, they may be a potential detection index. After tumor initiation, tumor cells could be analyzed to identify CSCs, and a CSC therapeutic strategy, whether alone or in combination with another therapeutic approach (like inhibiting angiogenesis), could be established. Subsequent determination of prognosis could be made by using CSC markers, and a revised therapeutic plan could be established to eradicate CSCs and cure the cancer completely.

Until now, cancer stem cell theory has not been proven to be a global theory in explaining any cancer initiation. Thus, determining the applicable scope of cancer stem cell theory should be one of the most predominant tasks in cancer therapy research for a long time. Determination of the origin of CSCs and identification of specific CSC surface biomarkers should also be explored at present.

CSC-targeting therapy provides a new approach to cancer treatment. Although CSC research is still in its infancy and much of the screening and targeting strategies should be improved, this field of study is expected to bring new opportunities to cancer exploration and cancer therapy.

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