MINI-REVIEW

Nanomedicine and Liver Cancer Stem Cells

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Abstract: In recent years, overwhelming experimental and clinical data demonstrate the existence of a unique subpopulation of highly malignant tumor cells termed as cancer stem cells (CSCs). They have been found in many solid tumors, including liver cancer. Liver CSCs may be known as the source of malignant cells, the reason for resistance to chemotherapy and radiotherapy, and the cells source of distant metastases. Therefore, new and effective treatment strategies targeting liver CSCs are urgently needed. Nanomedicine-based nanotechniques and biomaterials have emerged as some of the most promising carrier systems for medical imaging and drug delivery. The advances of nanomedicine result in the concept of precision medicine and the opportunity for early diagnoses and highly-effective targeted therapy. This review will focus on the properties of liver CSCs, discuss the preclinical and clinical available applications of nanomedicine, and explore the future implications and challenges.

Keywords: Liver cancer stem cells, Nanomedicine, Nanotechnology, Biomaterials, Imaging, Targeted drug delivery

1 Introduction

For hematological malignancies and solid tumors, stem cell biology indicated that cancer stem cells (CSCs) lead toward histological and functional heterogeneity. CSCs have the capacity to self-renew, to produce heterogeneous progeny, to limitlessly divide, and to resist chemotherapy and radiotherapy[1-4]. The principal mechanism of therapeutic resistance is the upregulation of active transmembrane adenosine triphosphate-binding cassette transporter family members, which serve to pump drugs from CSCs. Initiation and progression of liver cancer have been identified by a highly malignant subpopulation referred to as liver CSCs[5-7]. The conventional cancer treatments, such as surgery, chemotherapy, and radiation, are limited to curing malignancy as well as preventing metastases and relapses[8,9]. Thus, targeting liver CSCs provides new impetus and shows great potential for tumor biology and clinical oncology[10-13].

Several liver CSCs markers that have been identified include CD133, CD90, CD105, CD44, CD13, CD45, and epithelial cell adhesion molecules (EpCAM)[14-16]. The malignant phenotypes of liver CSCs, such as highly invasiveness and treatment resistance, are functionally supported by these molecule markers. Therefore, the surface markers play an important role in the identification and eradication of liver CSCs[17-20].

Non-specific systemic drug distribution, inadequate drug concentrations reaching the tumor, and the limitation to monitor therapeutic responses were considered the grand challenges for cancer treatment. Better delivery efficiency and greater targeting selectivity are the main goals in the development of imaging agents or therapeutic formulations. These provide not only improvement to medicine development but also offer entirely...
new tools and capabilities, since nanotechnology is a promising technology in many aspects\cite{21-23}. Nanomedicine is application of nanotechnology in biological systems, including treatment, diagnosis, controlling, and monitoring. The overall aims of nanomedicine are accurate and early diagnosis, effective treatment without side effects, and non-invasive evaluation of treatment efficacy. Rational delivery and targeting of therapeutic and diagnostic agents are the key aspects in nanomedicine\cite{24-30}. A variety of nanomaterials with various sizes and modifications, such as organic polymers, carbon, noble metal, and DNA, can provide promising means for developing treatments for liver CSCs\cite{27-28}.

In the future, nanomedicine that takes the advantage of excellent properties will offer better strategy and precision for targeted and controlled elimination of liver CSCs. The recent progress of nanomedicine for liver CSCs was summarized in this review, encompassing the diagnostic application of nanomedicine, how nanomedicine is used as drug delivery systems to increase treatment effect, and how nanomedicine will be further developed to improve functionality.

## 2 Nanomedicine for diagnosis

Traditional imaging approaches, including computed tomography and magnetic resonance imaging (MRI), focus mainly on delineating morphological features, such as tumor size, anatomic location and extent, spatial resolution, and contrast at various levels. Recently, a new field which is termed molecular imaging has emerged, and this technology focused on visualization of biological events and processes in living systems. Molecular imaging technologies, such as positron emission tomography, optical imaging and single-photon emission tomography, show high sensitivity and non-invasive characteristics in tumor detection\cite{29-31}.

Nanocarriers are regarded as promising approaches for non-invasive tumor imaging. Multifunctional nanocarriers loading contrast agents offer the opportunity of targeted tumor imaging. In comparison with conventional imaging probes, nanocarriers have both more functional ligands and greater surface areas for improvement of diagnostic effects. To obtain the desired optical and magnetic properties for molecular imaging, nanocarriers with specific sizes can be synthesized under controlled conditions\cite{32-34}. This makes it possible to design smart nanocarriers, such as multimodality imaging probes, target-specific contrast agents, and reagents for combined imaging and treatment.

Not only the targeted nanocarriers exhibited a significant therapeutic effect but also they could be monitored by non-invasive imaging. Winter et al. reported that integrin-targeted paramagnetic nanocarriers could detect angiogenesis using MRI in very early atherosclerotic disease. This novel agent allowed quantification of disease extent; meanwhile, it could also deliver therapeutic doses of an anti-angiogenic drug. To monitor the effect longitudinally, MRI scans were carried out using diagnostic version of targeted paramagnetic nanocarriers following treatment\cite{21,35}.

CD133, CD90, CD105, CD44, CD13, CD45, and EpCAM were defined as the surface markers for liver CSCs. These markers helped identify liver CSCs, which displayed exclusive features of tumorigenicity and metastasis. To employ these markers in the identification of liver CSCs, nanoparticles (NPs) loading imaging agents can be decorated with ligands, such as antibodies against different surface markers, which are able to induce efficient receptor-mediated internalization to improve site-specific recognition relative to free agents\cite{36,37}.

## 3 Nanotherapeutics

At present, the potential therapeutic approaches targeting liver CSCs may include ablating the expression of surface markers, inhibiting self-renewal and/or inducing differentiation, disruption of key signaling pathways, micro-RNA or siRNA targeting, and increasing the sensitivity to chemotherapy\cite{38-40}. However, complex crosstalk among gene regulatory pathways in liver CSCs provides a major barrier in implementing these approaches in the clinical setting\cite{41}.

Over the past few decades, biodegradable polymeric NPs have shown the potential as one of the most promising nanocarrier systems for various anticancer drugs relative to free drugs. The advantages of such a formulation include the high capability to cross physiologic barriers, facilitated extravasation into the tumor, targeted delivery, sustained drug action on the lesion, controlled drug release, and reduced systemic side effects\cite{42-47}. With the goal of active targeting liver CSCs, conjugation of ligands with polymeric carriers which was considered an effective strategy was widely applied. These ligands can selectively recognize antigens or receptors that are usually uniquely or abundantly expressed on cancer cell surface\cite{48-52}. Compared with conventional drugs, the promising efficacy of conjugated drugs was demonstrated in many preclinical and clinical trials\cite{53}. Gong et al. reported that salinomycin (SAL)-loaded nanoliposomes + doxorubicin-loaded nanoliposomes (DLN) as well as SAL and DLN exhibited better inhibitory rate and significantly decreased the percentage of liver CSCs in vivo in a tumor regression study\cite{54}. Wang et al. reported that disulfiram (DS)-loaded poly lactic-co-glycolic acid (PLGA) NPs were developed for protecting from drug degradation in the bloodstream. The characteristics of NPs (i.e., drug loading content, encapsulation efficiency, and controlled release rate in vitro) were very satisfactory. DS-PLGA NPs showed superior inhibition of liver CSCs. The remarkable synergistic cytotoxicity between DS-PLGA NPs and fluorouracil or sorafenib was observed. DS-PLGA NPs showed promising anticancer effect and antitumor metastatic.
efficacy in liver cancer animal model[55]. Wang et al. prepared SAL-loaded PEG-ceramide nanomicelles (SCM) for targeting liver cancer cells and CSCs. SCM exhibited enhanced cytotoxic effect on and increased activity of inducing apoptosis in liver cancer cells and CSCs[56].

We developed PLGA NPs-containing paclitaxel decorated with an anti-CD133 antibody targeting liver CSCs using carbodiimide chemistry. NPs showed high encapsulation efficiency, suitable particle size, and spherical morphology. Depending on the selective elimination of CD133 positive subpopulation, NPs significantly improved therapeutic response. The data suggest that the novel NPs with excellent therapeutic efficacy are valuable candidates for targeting therapy[57,58].

4 Limitation in nanomedicine

It is well known that cancer develops in a multi-step carcinogenesis process and its progression involves numerous complex survival mechanisms, including sustained angiogenesis, evasion of apoptosis, invasion and metastasis, self-sufficiency in growth signaling, limitless replicative potential, and insensitivity to growth-inhibitory signals. Overwhelming research data demonstrated that CSCs, as a subset of the tumor cells, are eventually responsible for tumor initiation, progression, and recurrence. By means of the surface markers as tools, it becomes possible not only to identify liver CSCs but also to eradicate these cells. In CSCs model, treatment targeting CSCs provided only an opportunity to cure the patients. Depending on the surface markers that are distinctive of liver CSCs, these cells are fundamentally stem cell-like cells[59]. More studies are warranted to develop effective methods that allow accurate identification and procurement of liver CSCs.

Although many therapeutic drugs targeting liver CSC have been developed, their clinical significance has not been confirmed. Detection of CSCs-specific molecular signatures involving high therapeutic resistance is one of the possible valuable approaches targeting liver CSCs. In nanomedicine, development of nano-drug delivery systems is still under investigation, which is far from standardization and industrialization.

5 Outlook

Over the past several decades, nanomaterials and nanotechnology have been widely used in the biomedical field, introducing a new strategy for drug delivery, cell imaging, and targeted cancer therapy. Nanosystems with different compositions and biological properties are on the route to offering a novel approach in cancer diagnosis and treatment. Nanomedicine has been extensively investigated for targeting liver CSCs which have been recognized as an important therapeutic target. Nanomedicine has the potential as an effective approach to improve outcomes in patients with cancer. In the future, various nanocarriers, such as NPs, liposomes, micelles, dendrimers, quantum dots, and nanotubes, will be rationally developed and their delivery efficiency will be improved based on our understanding of their interaction with the targeted cells and biological environment.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

References


