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Review

Nanomedicine-mediated cancer stem cell therapy

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ABSTRACT

Circumstantial evidence suggests that most tumours are heterogeneous and contain a small population of cancer stem cells (CSCs) that exhibit distinctive self-renewal, proliferation and differentiation capabilities, which are believed to play a crucial role in tumour progression, drug resistance, recurrence and metastasis in multiple malignancies. Given that the existence of CSCs is a primary obstacle to cancer therapy, a tremendous amount of effort has been put into the development of anti-CSC strategies, and several potential approaches to kill therapeutically-resistant CSCs have been explored, including inhibiting ATP-binding cassette transporters, blocking essential signalling pathways involved in self-renewal and survival of CSCs, targeting CSCs surface markers and destroying the tumour microenvironment. Meanwhile, an increasing number of therapeutic agents (e.g. small molecule drugs, nucleic acids and antibodies) to selectively target CSCs have been screened or proposed in recent years. Drug delivery technology-based approaches hold great potential for tackling the limitations impeding clinical applications of CSC-specific agents, such as poor water solubility, short circulation time and inconsistent stability. Properly designed nanocarrier-based therapeutic agents (or nanomedicines) offer new possibilities of penetrating CSC niches and significantly increasing therapeutic drug accumulation in CSCs, which are difficult for free drug counterparts. In addition, intelligent nanomedicine holds great promise to overcome pump-mediated multidrug resistance which is driven by ATP and to decrease detrimental effects on normal somatic stem cells. In this review, we summarise the distinctive biological processes related to CSCs to highlight strategies against inherently drug-resistant CSCs. We then focus on some representative examples that give a glimpse into state-of-the-art nanomedicine approaches developed for CSCs elimination. A perspective on innovative therapeutic strategies and the potential direction of nanomedicine-based CSC therapy in the near future is also presented.

1. Introduction

Historical studies have demonstrated that malignant tumours contain a rare population of cells with differences in their self-renewal capacity and long-term proliferation potential, as well as their ability to adaptively transfer tumours on transplantation [1–3]. Experimental evidence supporting the cancer stem cells (CSCs, also known as tumour-initiating or tumour-propagating cells) hypothesis was first generated in 1997 by Dick's group, who documented that human acute myeloid leukaemia (AML) was driven by a small fraction of $CD34^{+}/CD38^{-}$ leukaemic stem cells capable of transferring the disease to severe combined immunodeficiency disease (SCID) recipient mice [4,5]. Increasing data over recent years have indicated the existence of CSCs in a broad spectrum of solid carcinomas, including breast [6,7], brain [8], lung [9], colon [10–12], liver [13], and pancreatic cancers [14], based on their efficient tumour-initiating capabilities upon xenotransplantation into mice after isolation from primary tumours. Critics have argued that previous studies examined the existence and function of CSCs using transplantation models but not in a natural settings [15]. However, studying the genetically engineered mouse model, three different groups have independently provided strong and direct evidence for the presence of stem cell activity across three different types of solid tumours – skin, intestinal, and brain tumours – using

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a genetic lineage tracing strategy [16–18].

Compelling evidence suggests that CSCs play a crucial role in tumour progression, therapeutic resistance, metastasis and recurrence in multiple cancers. Current failure in cancer treatment is not usually due to a lack of primary response or initial induction of remission, but to drug resistance and recurrence after therapy, in which CSCs are thought to have a crucial impact [19–24]. Both laboratory models and clinical studies indicate that CSCs often display the same phenotypes as multidrug-resistant (MDR) cells including a high level of expression drug efflux transporters, activation of anti-apoptotic signalling pathways, enhanced efficiency of DNA repair, a quiescent or slowly proliferating nature and reprogramming of metabolic processes [25]. Notably, treatment with conventional methods (including chemotherapy, radiotherapy and tumour-targeting agents) often results in an increase of CSCs fraction, making it more likely that these cells will survive and spread to distant lesions [19,26]. Tumour relapses are often observed after treatment with anticancer agents, which only kill bulk tumour cells while sparing drug-resistant CSCs [27–29]. Further preclinical and clinical studies are needed to definitively assess how CSCs respond to therapy, and development of effective therapeutic strategies against CSCs is needed to increase the efficacy of cancer therapy. Potential approaches to kill CSCs include targeting CSCs surface markers, inhibiting ATP-binding cassette (ABC) transporters, blocking essential self-renewal and survival signalling or destroying the tumour microenvironment (or niches) [30,31].

The CSCs hypothesis has attracted much attention due to its potential for discovery and development of CSC-related therapies. An increasing number of therapeutic agents which can kill CSCs have been screened or proposed over the past several years, such as salinomycin [32], curcumin [33], thioridazine hydrochloride [34], sulforaphane [35], miR-34a [36], and miR-130b [37]. Unfortunately, similar to other anticancer drugs (e.g. small molecule drugs, peptides and nucleic acids), most such agents have characteristics that limit their clinical applications, such as an off-target effect, poor water solubility, short circulation time, inconsistent stability, and unsatisfactory biodistribution as well as low therapeutic indices [38]. Nanotechnology-based drug delivery systems (e.g. dendrimers, liposomes, polymeric micelles, carbon nanotubes and metal nanoparticles), which have gained considerable commercial and translational attention in recent years, have shown significant promise in overcoming aforementioned limitations [39,40]. By careful control of components, size and surface properties, nanoparticles can carry large payload of multiple drug entities and improve pharmacokinetic and pharmacodynamic profiles, while simultaneously reducing detrimental side effects to normal tissues [41]. Successful examples of clinically approved nanocarrier-based therapeutic agents (nanomedicines) for cancer therapy include liposomal doxorubicin (Doxil®) [42], albumin-bound paclitaxel (Abraxane®) [43], and PEG-L-Asparaginase (Oncaspar®) [44]. In addition, more novel and sophisticated multifunctional nanoparticles are being introduced and evaluated [41], which has fuelled enthusiasm for the investigation and development of CSC-specific nanomedicines.

The successful development of therapeutic approaches that can deplet CSCs requires a comprehensive understanding of the characteristics of CSCs as well as the application of modern technologies for drug delivery [45]. In the past two decades, many proof-of-concept studies on applying this new modality to tackling the challenges posed by CSCs have demonstrated encouraging results. For instance, curcumin-loaded Nano-Curc™ (SignPath Pharmaceuticals, Inc., Pennsylvania, USA; 1.5% curcumin content) was able to significantly suppress anchorage-independent clonogenic growth and reduce the fraction of $CD133^+$ CSCs in glioblastoma [46]. In our recent work, using a polymer co-delivery system, doxorubicin and all-*trans*-retinoic acid were delivered to eradicate human breast cancer cells together with CSCs, resulting in enhanced anticancer efficacy compared with free agents [47].

Nanotechnology-based approaches have demonstrated significant potential in drug delivery, and an enormous number of CSC-targeting nanomedicines are being introduced, developed and evaluated in various preclinical studies. However, the path to successfully reach clinical application is still challenging and poses critical barriers to be addressed and plenty of room for improvement. In this review, we briefly discussed particular biological processes that are related to CSCs focussing on strategies against drug-resistant CSCs, followed by a summary of the latest developments in nanomedicine approaches for CSC therapy in recent literature. In addition, we highlighted promising future research directions for anti-CSC nanomedicine, including the development of more efficient delivery systems and the exploration of innovative therapeutic strategies based on the combination of nanotechnology and biomedicine.

2. The CSCs theory and strategies against CSCs

Modern genomic, proteomic and functional analytical techniques have significantly deepened our understanding of cancer molecular biology [48]. Accumulating studies of tumour heterogeneity and relevant mechanisms have confirmed the existence of a unique fraction of tumour cells that possess distinctive self-renewal, proliferation and differentiation capabilities, interchangeably called cancer stem (-like) cells (CSCs) or tumour-initiating cells (TICs) [49–51]. A number of specific cell surface markers and several intracellular dyes (e.g. Hoechst 33342 [52], PKH26 [7]) are now used for the identification or isolation of CSCs from haematopoietic malignancies and solid tumours. CSCs are believed to acquire self-renewal and differentiation capabilities, and can give rise to more differentiated derivatives, which largely comprise the bulk of tumour tissues. The origin of CSCs within solid tumours remains elusive, some studies indicate that they may originate from a series of naturally-occurring normal stem cells or from differentiated cells [53,54]. Several experiments also suggest the key role of epithelial–mesenchymal transition (EMT) programmes in generating cells with the traits of CSCs in various malignancies [32,55].

CSCs share many properties with normal stem cells and it is generally accepted that they are the driving force for tumourigenesis [51]. Since CSCs have intrinsic properties that render them a longer lifespan and resistance to conventional cancer treatments, including chemotherapy and radiotherapy, treatment is likely to further enrich the CSC population [24,56,57]. CSC-rich tumours are prone to proliferate and/or disseminate to distant lesions, leading to the development of metastases and relapse after the initial therapeutic success [28]. These features of CSCs pose major hurdles in current cancer therapy, and are now recognized as primary causes in cancer mortality (Fig. 1).

Given the urgent need for CSCs eradication in treating malignant tumours, intensive effort has been directed toward the development of strategies against CSCs and identification of therapeutic agents that can successfully kill CSCs [31]. For example, inhibition of ABC transporters overexpressed on the CSCs surface is believed to increase sensitivity to therapeutic agents. Both subtle surface marker differences and alterations in signalling pathways are alluring therapeutic targets. Altering the microenvironment (or niche) supporting CSCs also present a popular and efficient strategy. With increasing understanding of CSCs characteristics, strategies that are more novel are under evaluation, such as inhibition of autophagy and modulation of abnormal metabolism. A summary of popular CSC-targeting therapeutic strategies is listed in Fig. 2.