Review Article

Stem Cell INVESTIGATION

Cancer stem cells and evolving novel therapies: a paradigm shift

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Abstract: Accumulating evidence of stem-like cells/cancer stem cells (CSCs) has been gaining attention of cancer researchers over the last decade. Though many tumors harbor CSCs in their dedicated niches, identifying and exterminating those cells has proved to be difficult, due to their heterogenous nature, as the CSC phenotype vary substantially and may undergo reversible phenotypic changes. As a tumor propagation initiator, CSCs are considered as an exciting novel therapy for a better therapeutic outcome. This review discusses the major advances in the development of CSC-based therapies of most common cancers which includes lung, cervix and liver cancers.

Keywords: Cancer stem cells (CSCs); lung cancer; cervix cancer; liver cancer; nanoparticles (NPs); novel therapies

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Introduction

Cancer is an umbrella term covering a plethora of conditions characterized by unscheduled and uncontrolled cellular proliferation. As the average life expectancy in many countries steadily rises, so do cancer-related deaths, thus making cancer as most common causes of death in 21st century. Despite several debates on the causes of disease, the history of medicine teaches us the need for understanding the scientific basis before the development of successful therapy. The paradigm shift in cancer treatment, with surgery, radiotherapy and conventional cytotoxic chemotherapy for the past 20 years has made only a modest overall impact on mortality. Though, childhood cancers, testicular cancer and lymphoma can be cured, and the survival rates of breast and colorectal cancer have been improved through adjuvant drug treatment, majority of human cancers are difficult to treat, especially in their advanced, metastatic forms (1). There is thus a pressing need for novel and effective forms of systemic therapy.

As a result of the advanced research, evidences suggest that the relapse of the disease depends on the small subset of cells within the tumor, termed as cancer progenitor cells/cancer stem cells (CSCs) or cancer initiating cells (*Figure 1*).

Though intensively researched, much remains to be elucidated about their function in initiation and progression to metastatic disease states and resistance to conventional therapies. The self-renewal ability, aberrant multi-lineage differentiation potential and the 'stemness' property of CSCs is said to contribute, to the formation of the heterogeneous cellular population into major cell types observed in the corresponding tumor, which is resistant to ROS or DNA damage (1,2). Furthermore, occurrence and recurrence of highly aggressive cancer subtypes may transpire, owing to the accumulation of different genetic and/or epigenetic alterations in cancer progenitor cells during cancer progression, which in turn has inspired the design of innovative treatment strategies for most common types of cancers, including leukemia (3,4), breast cancer (5), colorectal cancer (6,7) and brain cancer (1,8) which now aims at exterminating CSCs rather than shrinking tumor bulk.

Since, recent evidence suggests that CSCs are resistant to radio and chemotherapy (9), the CSC model became the

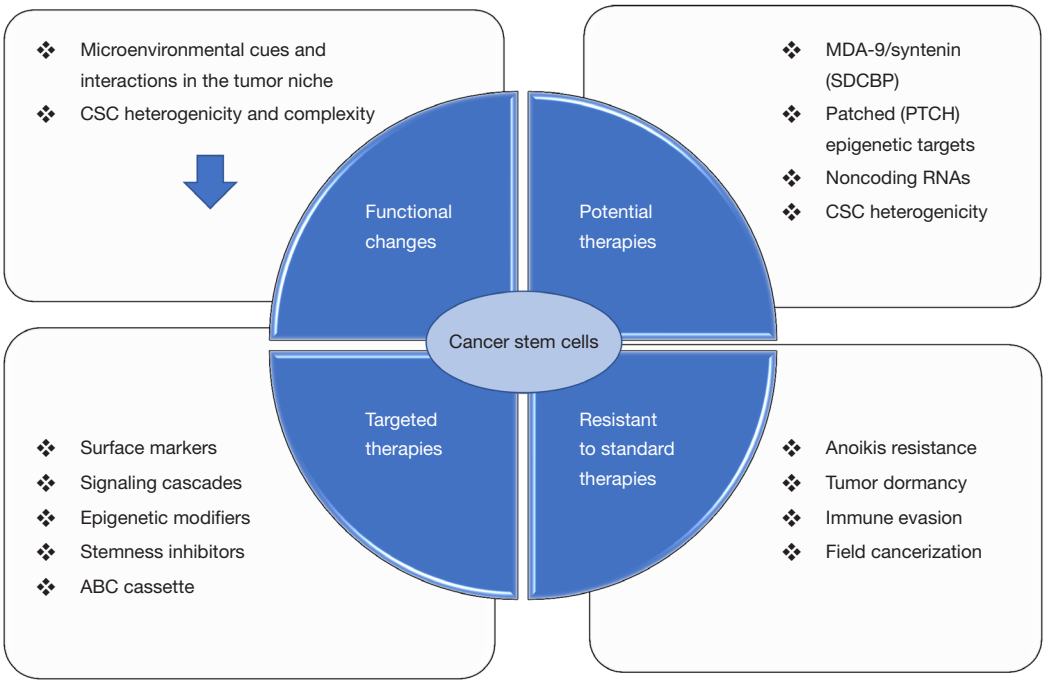

Figure 1 An overview of emerging therapeutic concepts in CSC biology. CSC, cancer stem cell; ABC, ATP-binding cassette.

foundation for new preventive and therapeutic strategies in cancer. Intensified understanding of CSC-derived heterogeneity, the asymmetric division of CSCs which enables the cells to generate differentiated progeny, will provide additional insights to efficiently eliminate CSCs through targeting CSC-marker, CSC-specific cellular signaling pathways, and CSC-microenvironment (10,11). The aim of this review is to focus on major advances in the development of CSC-based therapies of most common cancers which includes lung, cervix and liver cancers.

Lung cancer: the leading killer

Lung cancer, classified as non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), is the leading cause of cancer-related death with highest morbidity and mortality in the United States (12,13). Despite novel molecular therapies, the prognosis of NSCLC, which accounts for 85% of cases, has low treatment response rates and poor overall prognosis (1% estimated survival rate). If diagnosed early, NSCLC patients may benefit from surgery and result in a cure, but, SCLC are almost never diagnosed early, even after surgery rarely result in a cure.

Standard chemotherapy and radiotherapy, has reached a plateau of effectiveness in improving survival. Therapies targeting new blood vessels, treatments interfering with chemical signal required for cancer cell growth, treatments targeting the receptors like epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) are being tried (14,15). Cascone *et al.*, has reported that the combined use of EGFR-tyrosine kinase inhibitor erlotinib and the humanized VEGF receptor monoclonal antibody bevacizumab in advanced, chemotherapy-refractory NSCLC has shown promising results (16).

Arrival of targeted therapies harboring BRAF, MET, HER2 and RET alterations, understanding early epigenetic targets and advances in understanding the role of DNA methylation and histone modifiers have established new standards of care for defined molecular subsets of NSCLC (17). In lung cancer, CSC populations have been identified and enriched in multiple phenotypic sub-population, such as drug-resistant side population (SP) (18) CD133pos cells (19,20) and ALDH high cells (21,22) and exhibit plasticity. An independent study demonstrated an increase in the fraction of CD133 positive lung cancer cells present after treatment of mice carrying human lung cancer xenografts with cisplatin (23). CSC possess several mechanisms to overcome irreversible damage by cytostatic

drugs, thereby has been claimed as chemo resistant. Strong evidence for the presence of drug-resistant and highly regenerative tumor cells in NSCLC has been reported (24,25). However, Chandrakesan *et al.*, has reported that the combination therapy of siDCLKL1 (doublecortin like kinase 1) with cisplatin can overcome cisplatin induced drug resistance thus making DCLK1 targeted therapy an attractive tool for combating NSCLC (26). Also, novel imaging techniques are being developed to identify and track these stem cells in their natural niche may provide better understanding on the significance of CSCs in drug resistance, tumor regeneration and metastasis.

CSC drugs targeting stem-like traits of cancer cells could be effective in controlling refractory EML4-ALK+ NSCLC (25), along with the signaling pathways which are critically involved in CSC regulation. Currently, several early phase studies analyzing the efficacy of Wnt, Notch, MAPK and Hedgehog pathways as well as the PI3K/AKT/mTOR signal transduction axis are in progress.

Though, several fundamental results on lung stem cells were derived from murine models, whether the findings can fit human conditions, are still a debate. Meanwhile, the therapeutic management of patients with advanced NSCLC is an ongoing challenge and several novel agents targeting cancer are under investigation.

Cervical cancer and CSCs

Among the most commonly diagnosed cancers in women, cervical cancer accounts for 7.9% and occupies the second and third position as the leading cause of cancer-related death worldwide. Whilst the treatment strategies include surgery and chemotherapy, it doesn't provide a permanent cure. Whereas, radical surgery for advanced stage affects the child bearing ability of the patient, along with risk of recurrence (27). Currently, hysterectomy and radiation therapy are used to treat and cure cervical cancer at early stage (28). The gene expression profiling of cervical cancer cells has shown aberrant methylations of the CpG island within the promoters of several tumor-suppressor genes including p53, which is normally involved in the positive regulation of apoptosis and negative regulation of cell growth and migration (29). Studies have shown that approximately 90% of CIN3 (abnormality of squamous cells lined in ectocervix) and cervical cancer arise within or very near the SC junction, where the malignant lesions are initiated by an interaction between human papilloma virus (HPV) infection and the genetic and epigenetic alteration of healthy stem cell (30). These CSCs bypass drug cytotoxicity, by using Adenosine triphosphate (ATP)-dependent protein family's efflux pumps (31), thereby marking ATP-binding cassette sub-family G member 2 (ABCG2) as a potential target. Studies has also revealed several other markers along with ABCG2, which includes ALDH1A1, CD133, CK-17, p63+, AII+, CD49F, OCT4, osteopontin (OPN), SOX-2, NANOG, CD44, C-KIT (32). However, the detailed mechanisms responsible for higher expression of ALDH1A1 in cervical cancer stem cells (CCSCs) are largely unknown. Liu *et al.* found that the cervical cancer cells, which were resistant to radiotherapy, exhibited a higher percentage of surface markers CD44+ and CD24+ (33). Studies also showed a critical role of AP-1, a key regulator for expression of HPV oncogenes, in mediating chemo- and/or radioresistance (34,35). Tyagi *et al.*, have targeted AP-1 with herbal derivative curcumin to induce radio-sensitization and downregulated c-Fos, c-Jun and upregulated Fra-1 for effective cancer treatment (36).

Though CSC-targeted therapies have been intensively studied, specific CCSC targeted therapies are very limited. Likewise, dual-targeting strategies, for example VS-5584, as a potent and selective dual inhibitor of mTORC1/2 and class I PI 3-kinases (PI3K), which specifically targets human CSCs have been reported (37), however, no studies have yet reported on the use of dual-targeting to treat CCSCs.

Liver cancer and CSCs

Liver cancer, the fifth most prevalent cancer and third leading cause of cancer related death is associated with hepatitis C virus (HCV) infection along with HBV. Among primary liver cancers, hepatocellular carcinoma (HCC) represents the major histological subtype, accounting for 70–85% of cases of primary liver cancer (38). Intrahepatic cholangiocarcinoma (ICC) is the second most frequent type of liver cancer, and its incidence has been increasing. Reports say that Western's population develops HCC in cirrhotic liver while noncirrhotic liver cancer develops in 50% of Asian countries. Metabolic syndrome is said to be an additional risk factor for HCC development (39).

Among others, therapeutic options and prognosis of the patients mainly depends on the stage on the presentation, based on several prognostic factors, which includes tumour size, number of the lesions, liver remnant function. Several markers including lens culinaris agglutinin-reactive AFP (AFP-L3), des-carboxyprothrombin (DCP), glypican-3 (GPC-3), OPN, and several other biomarkers (such as

squamous cell carcinoma antigen immunoglobulin M complexes, alpha-1-fucosidase (AFU), chromogranin A (CgA), human hepatocyte growth factor, and insulin-like growth factor (IGF) have been proposed for the early detection of HCC (40). Though none of them is optimal, when used together, their sensitivity in detecting HCC may increase.

Earlier stages of HCC are treated with resection or liver transplantation; however, tumor recurrence rate is still high up to 70%. Takayama *et al.* has proposed that adoptive immunotherapy, anti-CD3 and IL-2 stimulated autologous T lymphocytes infused in HCC patients may significantly improve postsurgical recurrence-free survival (41). Radiofrequency ablation (RFA), microwave ablation (MWA) or transarterial chemoembolism (TACE) were used to treat the intermediate stages. For advanced patients with large non-resectable lesions, Sorafenib is the standard of care. Sunitinib malate, an oral multikinase inhibitor targets several tyrosine kinases receptors, such as VEGF-1/2 and PDGFR-a/b, and is implicated in HCC proliferation and angiogenesis. However, sunitinib seems to have more side effects for its toxicity in HCC. Along with multikinase inhibitors, MET inhibitors, Antiangiogenic agents and mTOR inhibitors have been tested in HCC with marginal efficacy to date (42).

Recent insights into the molecular pathogenesis of HCC have identified several aberrant signaling pathways that have served as targets for novel therapeutic agents. Several pathways are now implicated in hepatocarcinogenesis and agents that target these pathways continue to be developed. For example, RAS/RAF/MAPK pathway is typically activated in HCC as a result of increased signaling induced from upstream growth factors and due to inactivation of tumor suppressor genes (43). Though Sorafenib, significantly inhibit RAS/RAF/MAPK pathway, the heterogenicity of these cancers may warrant a combination therapy for advanced stage HCC. Several reagents are being tested targeting novel signaling cascades such as Wnt-β-catenin and Notch.

Lately, the focus of treatment has shifted to explore the possibilities of inhibiting liver cancer stem cells (LCSCs). Tumor markers have been a mainstay of identifying cancer cells in all tissues. Lui *et al.*, has reported that LCSCs can be recognized by multiple cell surface antigens including CD133, CD90, CD44, CD24, and the epithelial cell adhesion molecule (EpCAM) (44).

Doublecortin like kinase protein 1 (Dclk1) is considered to be an important target for the treatment of tumors of the liver, pancreas, and colon. Studies were able to show that these Dclk1+ cells possess features of cancer stem (initiating) cells (45-47). In addition to OCT4, c-myc, NANOG and Sox-9, zinc finger transcription factors have been reported to regulate liver CSCs features. ZIC2, has been demonstrated to be highly expressed in liver CSCs which regulates and maintain liver CSC self-renewal by recruiting NURF complex to trigger OCT4 activation (48). miRNAs and lncRNAs (49) play an important role in regulating the properties of liver CSCs and therefore could be therapeutic targets. Epigenetic alterations, including DNA methylation, histone modifications, polycomb repressive complex (PRC), and chromatin remodeling complex function, are mechanisms that contribute directly to carcinogenesis and CSC regulation. Inhibiting histone deacetylase SIRT1, EZH2 can be a promising therapeutic approach to eradicate liver CSCs.

Conclusions

Accumulating studies, over the decade, supports the existence of CSCs in many cancer types, thus modifying our perception of cancer cure. Though complicated, new insights in to stem cell biology helps us to understand the features and behaviors of CSCs. Development of new technologies, opens up many avenues for analyzing CSCs in their intact environment. For example, CSCs targeting nanoparticles (NPs) is the topic of recent investigations, where the NPs is either with a ligand/cytotoxic anticancer drug/a chemosensitizer (such as ABC transporter inhibitor) or an imaging agent which facilitates tumor diagnostics. However, the identification of strategies that exploit the unique characteristics of CSCs requires further study and the cooperation of multidisciplinary areas.

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Footnote

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