

Review Paper

Targeting Cancer Stem Cells: A Solution to Cancer Therapy

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ABSTRACT

Over the past several decades, accelerating scientific and technological advances have enabled researchers to make a great quantity of knowledge in the field of cancer biology. Numerous genes, mutant alleles, proteins, and signalling networks involved in the initiation and progression of cancer have been identified and some of the mechanisms deliberating resistance to therapy. Because of the limited efficacy of presently available treatment modalities, the cancer results to death and distress. One of the most important and complicated topics about the cancer is cancer stem cells (CSCs). The CSCs are immortal tumor-initiating cells that share some characteristics with normal stem/progenitor cells. Some of their important characteristics are self-renewal and multilineage differentiation. Since CSCs have potential resistance to chemotherapeutic agents as well as radiation therapy, it makes a serious challenge for current cancer treatments. There are various strategies for eradicating CSCs. Targeting of CSCs usually occurs by pharmacological targeting, immunotherapy and genetic targeting (miRNA, oncolytic virus). More recently, nanomedicine considerably extends the anticancer drugs, treatment strategies, and targeting CSCs. In this field, all currently available strategies could be divided into three major sections: Drug delivery targeting CSCs (nanocarriers such as nanoparticles (NPs), liposomes, micelles, nanotubes and nanogels), targeting genes of drug resistance and destruction the CSCs niches. In this review, we discussed some characteristics of CSCs and their therapeutic strategies.

Keywords: Cancer, Immunotoxins, Antigen, Ligand, Bioinformatics

The first words which come to our mind about cancer stem cells (CSCs) are “What are cancer stem cells?”. Recent studies have suggested that CSCs are immortal tumor-initiating cells that can self-renew with pluripotent capacity. There are several common characteristics between somatic stem cells and cancer stem cells such as they could self-renew, are highly regulated, differentiated, and resistant to

apoptosis, and have long lifespan, but some differences have been observed such as producing tumor metastasize to distant sites through CSCs while somatic stem cells produces mature tissue through migration to distant tissues (1, 2). thought to be the basis for tumor initiation, metastasis, development and recurrence (3). Besides, cancer stem cells have several features including (4-6):

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- 1) Self-renewal
 - 2) Multipotent differentiation
 - 3) Tumorigenic potential
 - 4) Expression of stem cell markers
 - 5) Enhanced invasiveness
 - 6) Proliferation as tumor spheres
 - 7) Radio resistance
 - 8) Chemo resistance
 - 9) Resistance to hypoxia
 - 10) Resistance to apoptosis
 - 11) Quiescence
 - 12) Expression of Sox2, Nanog, and Oct4 in CSCs
- Several pathways are involved in CSC self-renewal that is shown in table 1.

Table 1. CSC and self renewal (7)

Signalling Pathways	Type of Cancer
WNT	CML, AML, Breast Cancer
Hedgehog	Breast Cancer, Pancreatic Cancer, CML, Glioblastoma,
Notch	Colon Cancer, Breast Cancer, Glioblastoma
BMI1	Murine Acute Myeloid Leukemia, Breast Cancer, Head and Neck Squamous Cell Cancer, Glioblastoma, Acute Myeloid Leukemia
PTEN	Murine Leukemia, Breast
BMP	Glioblastoma
TGF-B	Glioblastoma
Abbreviation: BMP, Bone Morphogenic Protein.	

CSCs have several biomarkers which are used in the isolation and characterization of them shown in table 2.

Table 2. CSC biomarkers (7-9)

Tumor Type	Marker(s) Used to Enrich for CSCs
Acute Myeloid Leukemia	⁻ CD38 ⁺ CD34
Breast	⁺ ALDH1 ⁻ CD24 ⁺ CD44
Brain	⁺ CD133
Prostate	^{high} ₁ β ₂ α ⁺ CD133 ⁺ CD44
Head and neck	⁺ CD44
Colon	⁺ CD44 ⁺ ALDH1 ⁺ CD133 EpCAM ^{high}
Pancreas	⁺ CD24 ⁺ CD133 ⁺ CD44 ⁺ ESA
Mesenchymal	Side Population
Lung	⁺ CD133
Liver	⁺ CD90
Melanoma	⁺ ABCB5
Ovarian	CD133

ATP-binding Cassette

ATP-binding cassette (ABC) transporters are membrane transporters that can pump different dissimilar and structurally unrelated small

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molecules (such as dyes and cytotoxic drugs) out of cells through ATP hydrolysis. Cancer stem cells and normal stem cells appear to express high levels of ABC transporters. This phenomenon could contribute to multi-drug resistance because various anti-tumor drugs can be pumped out, thereby resulting in low intracellular drug concentrations (10).

There are many mechanisms causing resistance of CSC including:

1. Modulation of Cell Cycle Kinetics
2. Habitation in Hypoxic Niches
3. Proficient Mechanisms of DNA Repair
4. Relative Resistance to Oxidative or DNA Damage
5. Intrinsic Expression of Anti-Apoptotic Molecules
6. High Expression of Multidrug-Resistance-Type Membrane Transporters
7. Chemoresistance of Cancer Stem Cells Due to Quiescence
8. Chemoresistance of Cancer Stem Cells Due to Aldehyde Dehydrogenase Activity (10, 11)

Different strategies that targets cancer stem cells including:

1. Suppressing proliferation of CSCs
2. Destroying CSC niche

3. Inducing the differentiation of CSCs
4. Inducing apoptosis of CSCs
5. Increasing sensitivity of CSCs to radiotherapy and chemotherapy (12).

How therapeutic strategies target cancer stem cells?

There are several mechanisms:

Pharmacological Targeting

Small molecule inhibitors have shown promising results when are used alone or in combination to target slow growing chemo- and radio-resistant CSCs. Several strategies have been employed including targeting signalling pathways that affect chemo- and radio-resistance to CSCs, thus increasing their susceptibility to conventional therapies (13).

Immunotherapy

Cancer stem cells have been associated with immunosuppressive properties (14), which are likely a critical part of the mechanism which provides the cells with tumor-promoting and immunomodulatory characteristics. Understanding the many different immunosuppressive pathways in CSCs allows for a more effective design of therapeutic elimination strategies (13).

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Conclusion

The identification of CSCs and the recent knowledge about their ability to resist common radio- and chemotherapy have urged a number of new targeting strategies to attack this rare but extremely important tumor subpopulation in order to eradicate cancer. It is necessary to mention focusing on CSCs' markers and related signaling pathways, have been also useful tools to find appropriate therapies. However, the CSC paradigm has provided exciting novel venues to improve cancer treatment by lowering recurrence and metastasis, which are considered to be the main cause of most cancer mortalities.