Cancer Stem Cells

Dito Anurogo[1,2]
[1]International PhD Program for Cell Therapy and Regeneration Medicine (IPCTRM), College of Medicine, Taipei Medical University (TMU), Taipei, Taiwan
[2]Fakultas Kedokteran dan Ilmu Kesehatan, Universitas Muhammadiyah, Makassar, Indonesia

ABSTRACT

This mini-review will discuss Cancer Stem Cells (CSCs) on their definition, history, characteristics, models, origin, tumorigenesis, targeting Cancer Stem Cells with nanomaterials, niche interactions, CSCs therapeutics, vaccination, the role of autophagy in CSCs, artificial intelligence, and clinical trials targeting CSCs.

Keywords: Cancer Stem Cells

ABSTRAK

Mini review ini membahas sel punca kanker (*Cancer Stem Cells*), meliputi: definisi, sejarah, karakteristik, model, asal-mula, tumorigenesis, menarget CSCs dengan nanomaterial, interaksi *niche*, terapeutik berbasis CSCs, vaksinasi, peran autofagi pada CSCs, kecerdasan buatan, dan uji klinik menarget CSCs. **Dito Anurogo.** ***Cancer Stem Cells***

Kata kunci: *Cancer Stem Cells*

Definition

Cancer stem cells (CSCs) are a subpopulation of cancer cells inside the cancer microenvironment niche that defines or constructs a reservoir of independent cells with the unique capability of self-renewal, multi-potent tumor-initiating properties and assembling various lineages of cancer cells.[1,2] The maintenance of CSCs is entirely controlled by the stroma and microenvironment.[3] CSCs can perpetuate themselves within the tumor growth via auto restoration with tumor-initiating potential.[4,5] CSCs are also known as tumor propagating cells (TPCs) and tumor-initiating cells (TICs).

History

The term CSCs was first introduced by Reya, *et al*, in 2001.[6] In 1963, Becker, *et al*, explained that some cells with self-renewal abilities could develop colonies or territories in the spleens.[7] In 1964, Kleinsmith and Pierce discovered a connection between cancer and stem cells. They succeeded in proving that single or particular stem cells can assemble malignant tumors. In the breast, normal stem cells and cancer stem cells have several pathways with active signaling.[8] In 1971, researchers discovered a small group of cancer cells in blood with extensive proliferation capabilities termed "leukemic stem cells". They successfully observed subpopulations of cells with identical features and properties in various types of solid tumors, such as breast cancer.[9]

Characteristics

Cancer stem cells (CSCs) have different characteristics from normal stem cells (NSCs). CSCs have various properties. For example, they have the tumorigenic capacity, are indefinite and extensive self-renewal, are rarely found in tumors, have abnormal karyotypes, and have identical surface markers as typical stem cells less mitotically active than other cancer cells, differ in phenotypical progeny.[10,11] Apart from self-renewal, CSCs also have essential roles

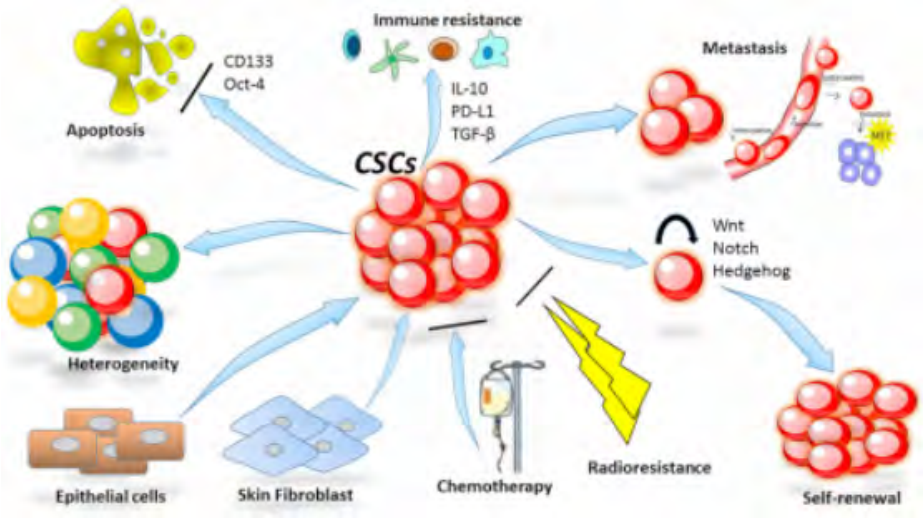

Figure 1. Cancer stem cell characteristics.[5]

Alamat Korespondensi *email: d151109004@tmu.edu.tw*

in regulatory and cellular processes, such as apoptosis, heterogeneity, metastasis, immune intransigence (resistance), and connected to chemoresistance and/or radioresistance (**Figure 1**).[5]

CSCs are generated from NSCs, progenitor, or precursor cells where epigenetic mutations exist (**Figure 2**).[3] Only CSCs can sustain and form a tumor and are impervious to standard therapies. Conventional therapies can reduce tumor size; if they can eradicate CSCs, they should be more powerful to annihilate the tumor. Developmental pathways such as Notch, Wnt/β-catenin, and Hedgehog perform instrumentally in cancers and are frequently transformed and are involved in CSCs regulation.[12] It is still an accustomed strategy to isolate CSCs by fluorescence-activated cell sorting (FACS) and scrutinize their biological features.[13]

Normal stem cells (NSCs) also have various properties, such as organogenic capacity, self-renewal, rarely found in normal adult tissues, having normal karyotypes, being able to be identified based on surface markers, being primarily silent, being able to engender normal progeny with restricted proliferative potential.[11,14]

Models

Basically, according to a non-stem tumor (traditional) model, every cell in a tumor can initiate a new tumor. Recently, based on models of tumor heterogeneity, there are two concepts. First, tumor cells have heterogeneous characteristics; most cells can proliferate extensively and create novel tumors. Second, tumor cells are heterogeneous, and only the CSCs subset can proliferate extensively and produce novel tumors.[15]

Somewhat similar is the heterogeneity model of cancer with two general models. First, all cancer cells are promising CSCs but have a low possibility of propagation in clonogenic assays. Second, only a tiny definable subset of cancer cells are CSCs that can propagate continually.[16]

Origin

The concept of CSCs can answer some enigmatic questions about cancer growth. However, it is important to know the origin of the CSCs; two fundamental factors need to be understood. First, a series of mutations are required for one cell to become cancerous. Second, stem cells need to overcome various genetic barriers to both proliferation and self-renewal capabilities.[4,17,18]

There are several theories on the origin of CSCs that lead to cancer. First, transforming stem cells, resulting in the growth and differentiation of the changed properties. Second is the transformation or renewal of an innate pool from previous precursors that regain properties with self-renewal characteristics. Third, the sequence of powerful mutations that change temporary-amplifying antecedent or extricated somatic cells between networks (so-called de-differentiation). Fourth, the process of circling bone-marrow-derived stem cells with the tissue-enduring cells.[5,16]

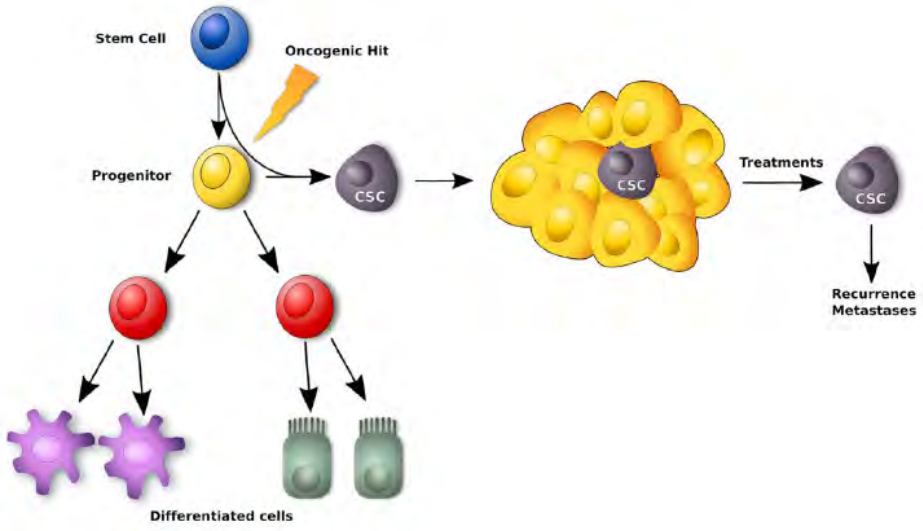

Figure 2. Model of CSCs theory. (CSC: cancer stem cell).[3]

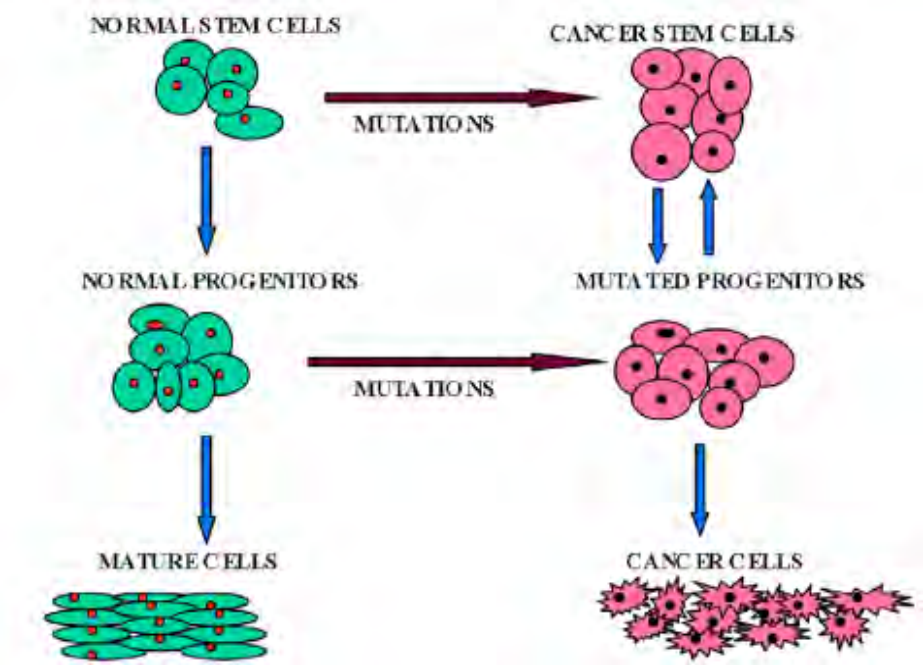

Figure 3. A simplified model of suggested hypothesis about the origin of the cancer stem cells. CSCs can develop when normal stem cells with self-renewing characteristics mutate and are transformed only by changing the proliferative pathway. It is also very likely that CSCs originate from multiple oncogenic mutations in limited progenitor cells that acquire self-renewal capabilities.[20]

It is highly unlikely that all mutations occur along with the lifespan of a progenitor or mature cell. Therefore, CSCs can come from either the progenitor cells or the self-renewing normal stem cells that have acquired self-renewal ability due to mutations (**Figure 3**).[19]

The current CSC paradigm is that a sparse population of tumor cells with several characteristics as normal stem cells (NSCs) such as self-renewal and stemness are behind the tumorigenesis (initial formation of a tumor) and the advancement of various cancers in humans.[13] While CSCs are found in multiple human cancers, it is crucial to know the origin of these cells. Reliable evidence proves that the plasticity of CSCs is a phenotypic characteristic and is influenced by a variety of protein signaling, a tumor-definite microenvironment, and specific or targeted transcription factors.[21,22]

This concept recommends that the various factors unique to each tumor have a dynamic balance and plasticity between cancer stem cells and non-cancer stem cells, thereby maintaining homeostasis in the subpopulation of tumor cells.[23] Homeostasis change through de-differentiation (**Figure 4**) because of natural occurrence or as an outcome of medical therapy results in tumor aggressiveness, since both cancer stem cells and the dedifferentiated non-cancer stem cells to drug-induced cancer stem cells are more resistant to the common radiation and chemotherapy management.[24]

Tumorigenesis

CSCs are the prevailing cells for tumor initiation. The tumor initiation assay is a standard and well-accepted method to ponder the self-renewal of CSCs.[26] Tumorigenesis is a process of oncogenic reprogramming. Many chromatin remodeling complexes are dysregulated in CSCs and cancer cells.[27] The chromatin remodeling becomes a demanding target for CSC and cancer eradication as a driver factor in tumorigenesis.[28] The SWI/SNF (mating type SWIt/Sucrose NonFermentable) chromatin remodeling complexes are muddled in CSC self-renewal and oncogenic reprogramming.[29] The SWI/SNF complex can be assembled into BRM-contained SWI/SNF complex and the BRG1-contained SWI/SNF complex. The BRG1-contained SWI/SNF complex is elevated in liver tumorigenesis, in as much as the BRM-contained SWI/SNF complex is dwindled.[30] This switch between BRG1-and BRM-contained SWI/SNF complex plays a fundamental aspect in liver CSC self-renewal and liver tumorigenesis.[31]

Targeting Cancer Stem Cells with Nanomaterials

New CSCs have been observed in nearly all cancer types, such as brain, colon, gastric, lung, pancreatic, prostate, etc. CSCs have several functional characteristics:

1. Specific signaling pathways and/or biomarkers can purify CSCs.
2. The capability to generate colonies in suspension culture conditions.
3. Resistant to radiation and chemotherapeutic agents.

Therefore, a considerable part of conventional treatments, e.g., radiation and chemotherapy, can execute most tumor cells but are unsuccessful in maintaining clinical results as resting CSCs can produce new colonies and invigorate tumors. Novel therapeutic approaches that selectively target cancer stem cells will advance cancer therapies.[32,33]

The CSCs can stimulate tumor development and be eminently resistant to typical treatments, such as radiotherapy and chemotherapy. Moreover, it leads to disease progression and the establishment of metastases. Thus, analyzing and selectively addressing signaling pathways and markers of CSCs are expedient therapeutic methods for managing numerous cancer types, regardless

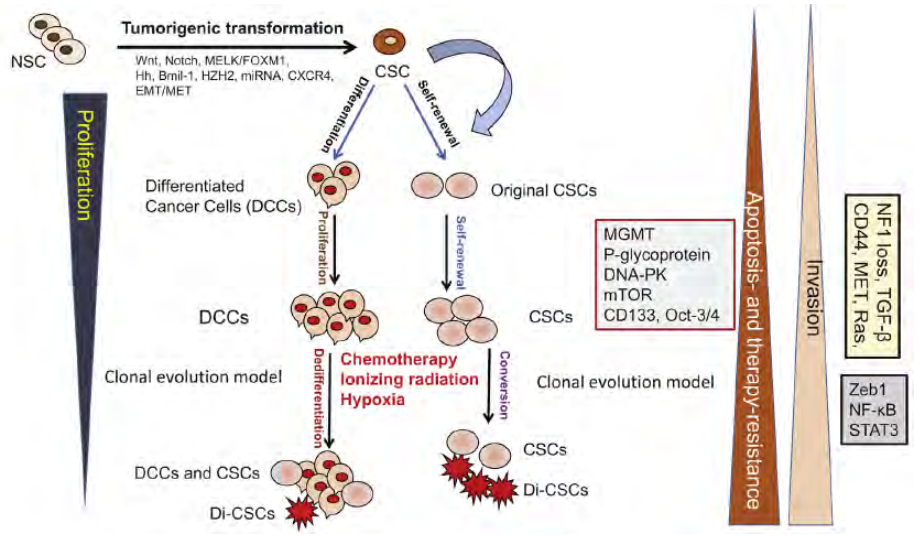

Figure 4. The implications cancer stem cells (CSCs) in the development and progression of tumors. CSCs are generated from the normal stem cells (NSCs) through tumorigenic transformation of several pathways such as Hh: hedgehog, epithelial-to-mesenchymal transition (EMT), and the reverse process mesenchymal-to-epithelial transition (MET). CSCs and drug-induced CSCs (Di-CSCs) are enriched following conventional chemotherapy treatment.[25]

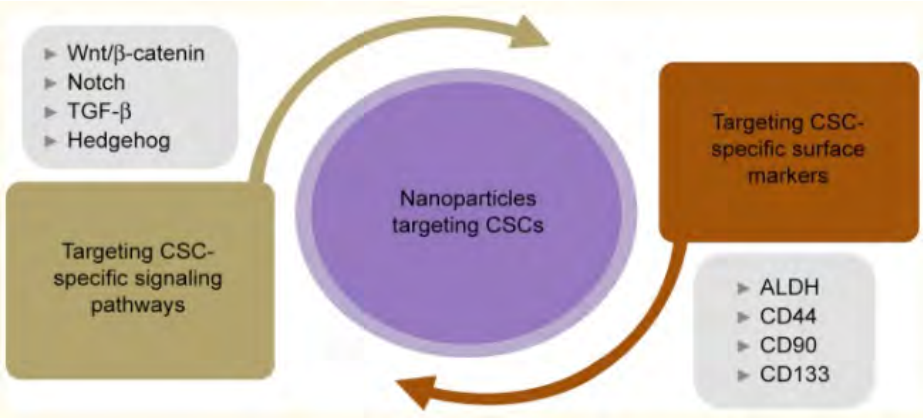

Figure 5. The promising roles of nanoparticles targeting CSC-specific surface markers or signaling pathways.[32]

of the elemental etiology.[34]

Presently, there is extensive excitement in the usage of nano-sized ingredients or materials for CSC-directed anticancer treatment. The modalities and novel therapy in the structure of nanoparticles (NPs)-targeting CSC-specific markers or signaling pathways are feasible or still being researched. The NPs' surface has been created to effectively and meticulously target directly to the CSCs.[32,34]

The schematic diagram encapsulates the promising aspects of NPS-targeting CSC-signaling pathways and specific markers in cancer treatments (**Figure 5**).[32]

Recognition of CSC is feasible by several markers, such as CD44 and CD90 and CD133, Aldehyde Dehydrogenases (ALDH) marker, and specific signaling pathways, such as Hedgehog, Notch, TGF-β (Transforming growth factor-β) to advance the therapeutic consequences and therapy strategies.[35]

Many types of research also recognized various kinds of NP-targeting CSCs, such as liposomes-based NPs, curcumin-based NPs, and NP-mediated hyperthermia. These nanoparticles (NP)-based therapeutic strategies support benefit over tiny molecule pharmaceutical agents-based therapeutic approaches.[36] Figure 6 exhibits the varied nanomaterial that targeted cancer stem cells.[35]

Niche Interactions

The complicatedness of the tumor microenvironment leads to the most destructive solid tumors with their mutual characteristics. CSCs vigorously reconstruct, inhabit in, and in turn also are controlled by several essential features of those niches, rising to a dynamic-heterogeneous population within numerical reliances and expansive diversity of intransigence systems (**Figure 7**).[37]

As long as directing a specific and targeted niche is adequate in several types of certain cancers, specifically in low-stadium tumors, therapy for many threatening solid tumors should be palliative. Moreover, their niches are neither static nor isolated. The vascularization area turns into a component of the hypoxic (low-oxygenated) area as many tumors outgrow their blood supply. Cells within the immune system endure throughout the different domains and display definite features and properties and functional interplay and communication towards niches.[37]

Durability is an essential element of a tumor model as a self-sustaining ecosystem. Thus, the intratumoral interactions driving that resilience will be a necessary target for effective treatment. For example, angiogenesis inhibitors could inhibit VEGF signaling (e.g., bevacizumab) or CSC-derived pericytes (e.g., via BMX inhibition).[37,38] Checkpoint inhibitors, e.g., PD-L1 or PD-1 antagonists (such as atezolizumab and nivolumab), have been used to target the bulk tumor of many solid cancers.[39] Still, CSC-specific strategies need the characterization and targeting of additional immunosuppressive or checkpoint mechanisms. Cytokine signaling, such as interleukin-6 (IL6) production by endothelial cells or interleukin- 4 by CSCs, mutually promotes CSC immunosuppression and maintenance.[40] Perivascular CSC-specific molecules, such as CD109 in glioblastoma CSCs, can be utilized with strategies such as HIF inhibitors to target CSCs across multiples niches.[37]

CSCs Therapeutics

Regardless of late improvements in cancer

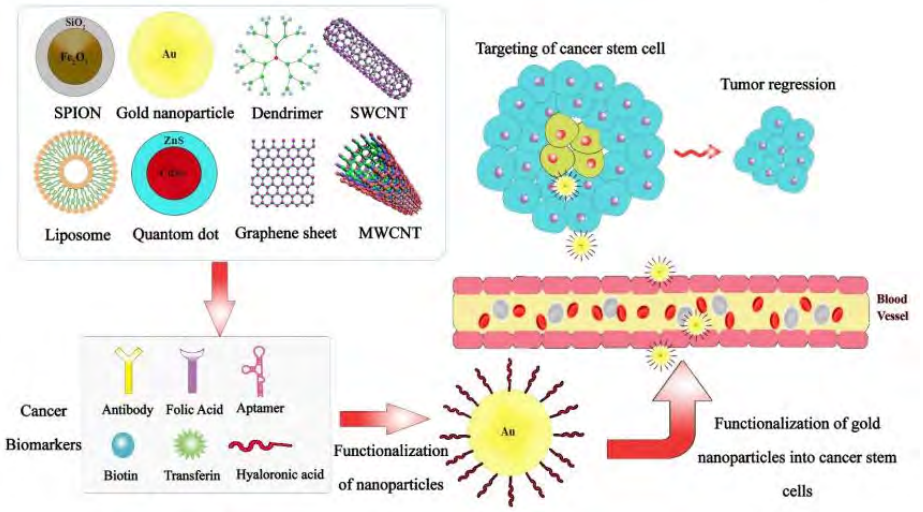

Figure 6. The schematic representation of targeting cancer stem cell via functionalized nanomaterial.[35]

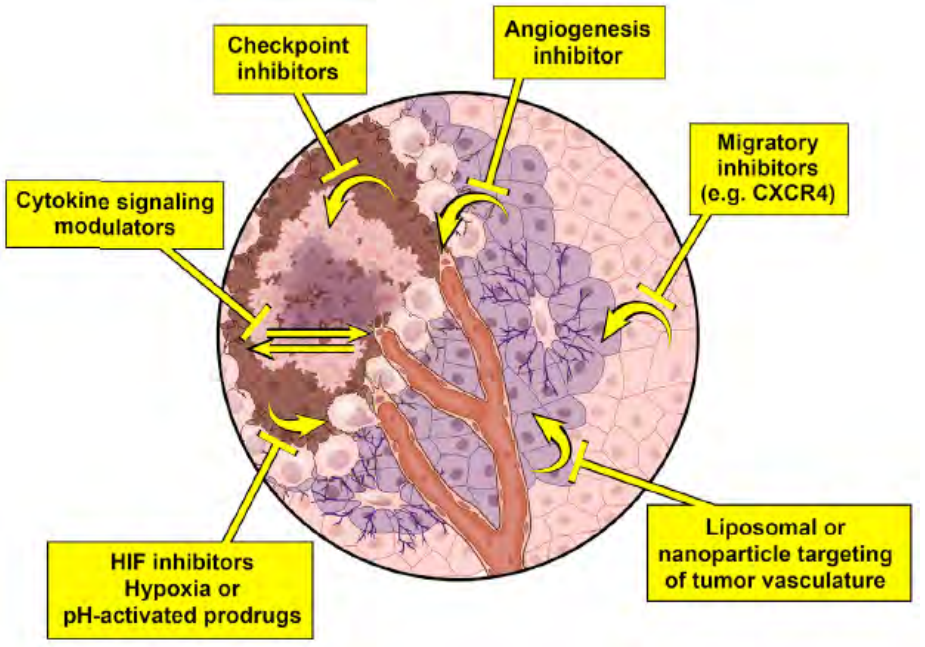

Figure 7. Effective therapeutic strategies should target CSC-Niche interactions[37]

treatments, chemoresistance and severe side effects are still problematic. Currently, it was affirmed that a small subpopulation of CSCs inside the tumor mass has self-renewal capacity and supports resistance to cancer treatments. CSCs are regularly referred to as Tumor Initiating Cells (TICs), which are answerable for metastasis. At the point when the epithelial-mesenchymal transition (EMT) happens, CSCs relocate through the lymphatic and blood circulation, self-renew, and differentiate into different kinds of anomalous cancerous cells via other elements (e.g., Notch, TGF-beta, SHh, and Wnt/beta-catenin signaling). Progressive alteration in the cytochemical properties of CSCs limits the improvement of viable therapeutics besides against usually shared biomarkers that recognize and detach CSCs from normal stem cells and cancer. Accordingly, focusing on the CSC microenvironment can be effective therapeutics to forestall metastasis interceded by CSCs, such as changing ECM deposition, adjusting the acidic microenvironment, and neutralizing hypoxic conditions. The unique energy metabolism (such as glycolysis and OXPHOS) of CSCs is hoped to be another promising candidate for therapeutics.[41] Table 1 summarizes promising compounds for forthcoming clinical CSC therapeutics.

Vaccination

A peculiar vaccination strategy can eradicate CSCs. ALDH-A1 and ALDH-A3 epitopes and advanced nanodiscs (NDs) carry these epitopes to induce ALDH-specific T cell

Table 1. Summary of potential compounds for future clinical CSC therapy[41]

Target		Name of Compound
Microenvironment	Acidosis/hypoxia	Anthracyclines, Anthraquinones, Acriflavine, Vinca alkaloids, Cobalt, MLN4924, PT2385, PT2399, PT2977
Intra-/intercellular molecules	Overall	Verapamil, SRI137892, scFvs, OMP-18R5, PTK7-ADC, LGK0974, ICG001, PRI-724, Merck-5, Ruxolitinib, Dasatinib, SK1-606, AZD9150, ML364, BI-2536
	Wnt/beta-catenin	Salinomycin, Piperine, Curcumin, Repertaxin, Parthenolide, 8-Quinolinol, Berberine, XAV939, IWR, IWP, Pyrvinium, iCRT-3,5,14, CCT036477
	HDAC	Valproic acid, Vorinostat, Panobinostat, Belinostat.
	TGF-beta	Galunisertib, LY2109761, SB431542.
Metabolism	Glycolysis	IAC-010759, ME-344, Etomoxir, perhexlline, DCA, AR-12, BX795, BX912
	OXPHOS	IAC-010759, ME-344, Etomoxir, perhexlline, DCA, AR-12, BX795, BX912

Table 2. Clinical trials targeting CSCs[56]

Drug name	Mechanism	Condition or disease	NCT Number	Current Status
Vismodegib (GDC-0449)	Hedgehog Pathway Inhibitor	Ovarian Cancer	NCT00959647	Completed
	Hedgehog Pathway Inhibitor	Basal Cell Carcinoma	NCT00959647	Completed
	Hedgehog Pathway Inhibitor	Metastatic Colorectal Cancer	NCT00959647	Completed
Sonidegib (LDE225)	Hedgehog Pathway Inhibitor	Medulloblastoma	NCT01708174	Completed
BMS-833923	Hedgehog Pathway Inhibitor	Leukemia	NCT02100371	Completed
MK-0752	Notch pathway inhibitors	Metastatic Breast Cancer	NCT00645333	Completed
RO4929097	Notch pathway inhibitors	Adenocarcinoma of the Pancreas	NCT01122901	Terminated
	Notch pathway inhibitors	Recurrent Adult Brain Tumor	NCT01122901	Terminated
Nirogacestat (PF-03084014)	Notch pathway inhibitors	Desmoid tumors/aggressive fibromatosis	NCT01981551	Active, not recruiting
Crenigacestat (LY3039478)	Notch signaling pathway	Neoplasms	NCT01695005	Completed
	Notch signaling pathway	Lymphoma	NCT01695005	Completed
Demcizumab (OMP-21M18)	Notch pathway inhibitors	Non-Small Cell Lung Cancer	NCT01189968	Completed
Ipafricept (OMP-54F28)	WNT pathway inhibitors	Stage IV Pancreatic Cancer	NCT02092363	Completed
	WNT pathway inhibitors	Pancreatic Cancer	NCT02050178	Completed
Vantictumab (OMP-18R5)	WNT pathway inhibitors	Metastatic breast cancer	NCT01973309	Completed
PRI-724	Wnt signaling pathway blocking	Advanced Solid Tumors	NCT01302405	Terminated
AVID 200	TGF-β inihibitors	Malignant solid tumor	NCT03834662	Active, not recruiting
Fresolimumab (GC1008)	TGF-β inihibitors	Metastatic breast cancer	NCT01401062	Completed
	TGF-β inihibitors	Stage IA Non-Small Cell Lung Carcinoma	NCT02581787	Recruiting
NIS793	TGF-β inihibitors	MPN (Myeloproliferative Neoplasms)	NCT02947165	Active, not recruiting
	TGF-β inihibitors	Lung cancer	NCT02947165	Active, not recruiting
	TGF-β inihibitors	Hepatocellular Cancer	NCT02947165	Active, not recruiting
	TGF-β inihibitors	Colorectal Cancer	NCT02947165	Active, not recruiting
	TGF-β inihibitors	Pancreatic Cancer	NCT02947165	Active, not recruiting
Ruxolitinib	JAK inihibitors	Metastatic breast cancer	NCT01348490	Completed
	JAK inihibitors	Myeloproliferative neoplasms	NCT01348490	Completed
AZD4205	JAK inihibitors	Advanced non-small cell lung cancer	NCT03450330	Completed
SAR245409	PI3K and mTOR inihibitors	Advanced or metastatic solid tumors	NCT01240460	Completed
Matuzumab (EMD 72000)	EGFR inhibitors	Non small cell lung carcinoma	NCT00753246	Completed

Clinical trials evaluating drugs for the selective inhibition of cancer stem cells in different solid tumors and hematologic malignancies.

responses.[42] When united with anti-PD-L1 IgG therapy, ND vaccination diminished the frequency of ALDHhigh CSCs in tumor tissues and exerted tenacious antitumor effects against multiple tumors recognized to harbor CSCs.[43] This endeavor performs the first scientific spectacle of an off-the-shelf nanoparticle-based vaccine strategy against CSCs and may lead to novel avenues for cancer immunotherapy against CSCs.[44]

Autophagy

Autophagy, a cellular self-digestion measure, is a novel cytoprotective interaction to expand tumor cell endurance under nutrient or growth factor starvation, hypoxia, and metabolic stress. It has a functional act in tumor advancement and arrangement. The tumor hypoxic surroundings may support the site for the enhancement or enlargement of the CSCs and ensuing expeditious tumor progression.[45]

Recently, CSCs have been deliberated to be one of the causes of deterioration of anticancer treatment, metastasis, recurrence, radioresistance, and chemoresistance. Autophagy may play a dual role in CSC-related resistance to anticancer therapy; it is responsible for cell fate determination and the targeted degradation of transcription factors through growth arrest. Autophagy advances drug resistance, dormancy, and stemness, and maintenance of CSCs. Various studies have also implied that autophagy can expedite the calamity of stemness in CSCs.[46]

Artificial Intelligence

Artificial intelligence (AI) enables machines to think like humans.[47] AI challenges in biomedicine involve multiple aspects, such as study documentation, study design, and sample size, clarity of scope and goals, statistical evaluation, integration of prior knowledge, model interpretability.[48] Recently, multiple omics-based AI diagnostic tools have already been clinically validated.[49] DeepMind's AlphaFold 2 is a significant advance in AI-based protein structure prediction.[50] Shortly, AI plays a prominent role in biomedicine, i.e., biomarker discovery, drug discovery, and digital health monitoring.[51]

AI was trained to utilize fluorescence images of the Nanog-Green fluorescence protein, the expression cultivated in CSCs, and the phase-contrast images.[52] The AI model segmented the CSC region in the phase contrast image of the tumor model and CSC cultures.[53] The possibility of mapping CSC morphology to the condition of undifferentiation was demonstrated using deep-learning conditional generative adversarial networks (CGAN) workflows.[54] Mitosis, nucleus, cell shape, and hemorrhage were distinguished automatically using convolutional neural networks (CNNs).[55]

Clinical Trials

Several clinical trials scrutinize the best cell target to fight cancer, including, but not limited to, CSCs, since CSCs are maintained by other cells containing tumor-associated macrophages (TAMs) (**Table 2**).[56]

Summary

Cancer stem cells (CSCs) are a subpopulation of cancer cells within cancer with the unique capability of self-renewal and multi-potent. Their maintenance is regulated by stroma and microenvironment. CSCs have diverse characteristics from normal stem cells. The fundamental factors in the origin of CSCs are mutations and various genetic barriers. Several clinical trials targeting CSCs were also revealed herein.

REFERENCES

1. Logtenberg ME, Boonstra J. Cancer stem cells and addicted cancer cells. Oncol Discov [Internet]. 2013;1(7). Available from: https://www.hoajonline.com/journals/pdf/2052-6199-1-7.pdf
2. Tirino V, Desiderio V, Paino F, De Rosa A, Papaccio F, Fazioli F, et al. Human primary bone sarcomas contain CD133+ cancer stem cells displaying high tumorigenicity in vivo. FASEB J. 2011;25(6):2022-30.
3. Papaccio F, Paino F, Regad T, Papaccio G, Desiderio V, Tirino V, et al. Concise review: cancer cells, cancer stem cells, and mesenchymal stem cells: Influence in cancer development. Stem Cells Translational Med. 2017; 6(12): 2115-25.
4. Sagar J, Chaib B, Sales K, Winslet M, Seifalian A. Role of stem cells in cancer therapy and cancer stem cells: A review. Cancer Cell Internat. 2007;7(1):9.
5. Atashzar MR, Baharlou R, Karami J, Abdollahi H, Rezaei R, Pourramezan F, et al. Cancer stem cells: A review from origin to therapeutic implications. J Cellular Physiol. 2020;235(2):790-803.
6. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature 2001;414(6859): 105-11.
7. Brunschwig A, Southam CM, Levin AG. Host resistance to cancer. Clinical experiments by homotransplants, autotransplants and admixture of autologous leucocytes. Ann Surg.1965;162(3): 416.
8. Kleinsmith LJ, Pierce GB. Multipotentiality of single embryonal carcinoma cells. Cancer Res. 1964;24(9):1544-51.
9. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci 2003;100(7):3983-8.
10. Najafi M, Farhood B, Mortezaee K. Cancer stem cells (CSCs) in cancer progression and therapy. J Cellular Physiol. 2019;234(6): 8381-95.
11. Rahman M, Jamil HM, Akhtar N, Rahman KMT, Islam R, Asaduzzaman SM. Stem cell and cancer stem cell: A tale of two cells. Progress in Stem Cell. 2016; 3(02): 97-108.
12. Singh SP, Singh R, Gupta OP, Gupta S, Bhatt MLB. Immunotherapy: Newer therapeutic armamentarium against cancer stem cells. J Oncol. 2020;2020:3963561.
13. Zhu P, Fan Z. Cancer stem cells and tumorigenesis. Biophysics Rep. 2018;4(4):178-88.
14. Topcul M, Topcul F, Cetin I. Effects of femara and tamoxifen on proliferation of FM3A cells in culture. Asian Pac J Cancer Prev. 2013;14:2819-22.
15. Marusyk A, Polyak K. Tumor heterogeneity: Causes and consequences. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 2010;1805(1):105-17.
16. Melo FDSE, Vermeulen L, Fessler E, Medema JP. Cancer heterogeneity—a multifaceted view. EMBO rep. 2013;14(8): 686-95.
17. Knudson A, S. LC Heredity and cancer in man. 1973.
18. van Gastel N, Scadden DT. Young haematopoietic stem cells are picky eaters. Cell Res. 2021;31(4):377-8.
19. Sell S. On the stem cell origin of cancer. Am J Pathol. 2010;176(6): 2584-94.
20. Jordan CT, Guzman ML, Noble M. Cancer stem cells. N Engl J Med. 2006;355(12):1253-61.

21. Safa AR, Saadatzadeh MR, Cohen-Gadol AA, Pollok KE, Bijangi-Vishehsaraei K. Glioblastoma stem cells (GSCs) epigenetic plasticity and interconversion between differentiated non-GSCs and GSCs. Genes Diseases 2015; 2(2): 152-63.
22. Safa AR, Saadatzadeh MR, Cohen-Gadol AA, Pollok KE, Bijangi-Vishehsaraei K. Emerging targets for glioblastoma stem cell therapy. J Biomed Res. 2016;30(1):19.
23. Walter RJ, Sonnentag SJ, Orian-Rousseau V, Munoz-Sagredo L. Plasticity in colorectal cancer: Why cancer cells differentiate. Cancers 2021;13(4): 918.
24. Arnold CR, Mangesius J, Skvortsova II, Ganswindt U. The role of cancer stem cells in radiation resistance. Front Oncol. 2020;10:164.
25. Safa AR. Oncogenomics. Cancer stem cells, apoptosis pathways and mechanisms of death resistance. Academic Press; 2019 .p. 89-101.
26. Zhou HM. Zhang JG, Zhang X, Li Q. Targeting cancer stem cells for reversing therapy resistance: Mechanism, signaling, and prospective agents. Signal Transduction and Targeted Ther. 2021;6(1): 1-17.
27. French R, Pauklin S. Epigenetic regulation of cancer stem cell formation and maintenance. Internat J Cancer [Internet]. 2020. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ijc.33398
28. Flavahan WA. Epigenetic plasticity, selection, and tumorigenesis. Biochem Soc Transact. 2020;48(4):1609-21.
29. Mittal P, Roberts CW. The SWI/SNF complex in cancer—biology, biomarkers and therapy. Nat Rev Clin Oncol. 2020;17(7): 435-48.
30. Zhou M, Yuan J, Deng Y, Fan X, Shen J. Emerging role of SWI/SNF complex deficiency as a target of immune checkpoint blockade in human cancers. Oncogenesis 2021;10(1):1-8.
31. Yang L, Shi P, Zhao G, Xu J, Peng W, Zhang J, et al. Targeting cancer stem cell pathways for cancer therapy. Signal Transduction and Targeted Ther. 2020;5(1):1-35.
32. Hong IS, Jang GB, Lee HY, Nam JS. Targeting cancer stem cells by using the nanoparticles. Internat J Nanomed.2015;10(Spec Iss):251.
33. Duan H, Liu Y, Gao Z, Huang W. Recent advances in drug delivery systems for targeting cancer stem cells. Acta Pharmaceutica Sinica B 2021;11(1):55-70.
34. Lu B, Huang X, Mo J, Zhao W. Drug delivery using nanoparticles for cancer stem-like cell targeting. Front Pharmacol. 2016;7: 84.
35. Asghari F, Khademi R,Ranjbar FE, Malekshahi ZS, Majidi RF. Application of nanotechnology in targeting of cancer stem cells: A review. Internat J Stem Cells 2019;12(2): 227
36. Wang H, He X. Nanoparticles for targeted drug delivery to cancer stem cells and tumor. Methods Mol Biol. 2018;1831:59-67.