MINI REVIEW OPEN ACCESS

Normal Cell Differentiation Potential of Cancer Stem Cells Without Reprogramming Pluripotent Factors: a Novel Strategy in Stem Cell-Based Therapy for Tissue Regeneration

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Abstract:

Stem cells hold great promise for tissue regeneration and have the potential to treat many incurable degenerative diseases. Cancer stem cells (CSCs), or cancer initiating cells, have the ability to self-renew and differentiate into heterogeneous lineages of cancer cells. Current stem cell therapies face limitations, such as limited stem cell sources, time consumption, tumor formation, and immune rejection upon allogeneic transplantation. Allogeneic stem cell treatments simplify stem cell manufacturing and reduce transplant time, but their therapeutic potential is limited by human leukocyte antigen (HLA)-matched donors. CSCs retain characteristics essential for tissue regeneration. However, several limitations hinder cancer stem cell reprogramming with pluripotent factors. The development of 3D culture models for tissue imitating extracellular matrix in cancer cell lines aims to enhance CSC enrichment. This mini-review focuses on a new strategy for treating incurable degenerative diseases involving *in vitro* and *in vivo* 3D cancer models and the induced differentiation of CSCs into mature normal cell types. This allows tissue survival without immune rejection and offers a safe alternative to cancer stem cell reprogramming with pluripotent factors. In conclusion, preservation and banking of allogeneic CSCs offer an alternative, readily available, and safe strategy that can be used to facilitate stem cell-based cell therapy.

Keywords — **Stem cell therapy, Cancer stem cells, iPSCs, Stem cell bank, Allogeneic transplantation, Differentiation therapy**.

I. INTRODUCTION

Cancer stem cells (CSCs), or cancer initiating cells, are a small population of cancer cells essential for tumor initiation, maintenance, metastasis, and recurrence, as well as having the ability to self-renew, proliferate, and differentiate into "heterogeneous lineages" of cancer cells [1-10]. CSCs are responsible for the chemoresistance, recurrence, and metastasis of tumors [11-13]. CSCs were first identified in human acute myeloid leukemia [14] and have also been identified in many other human solid tumors, such as breast [15], brain [16], ovarian [17], colon [18], skin [19], prostate [20], pancreatic [21], liver [22], and lung carcinomas [23], etc. CSCs form "niches" in the tumor microenvironment (TME), which mainly contains fibroblasts, immune cells, mesenchymal cells, endothelial cells, and extracellular matrix [24-27]. The niche is required for their survival and controls the self-renewal and differentiation of CSCs, similar to normal stem cells [28-30]. CSCs modulate their TME to escape immune detection through different mechanisms [31], and their ability to differentiate into heterogeneous lineages of cancer cells has been

demonstrated by many experimental models [32, 33]. CSCs avoid elimination by natural killer (NK) cells and cytotoxic T cells through various immune modulation mechanisms [34-36]. The CSCs of many tumors resist NK cell killing due to an "immunosuppressive" microenvironment [37, 38]. The tumor microenvironment weakens cytotoxic T cell function, reducing "immunogenicity" [39-41]. Treating cancers through the induction of differentiation has been an attractive and practical alternative to killing them through cytotoxicity [42-44]. However, the mechanisms responsible for differentiation vary among different tumor types [45-47]. Moreover, clinical studies reveal that CSCs are less tumorigenic or not tumorigenic at all after differentiation [48].

Stem cell therapy is a feasible clinical practice for the treatment of many "incurable degenerative diseases" [49], such as hematopoietic diseases [50], diabetes [51], cancer [52], eye diseases [53], stroke [54], neurodegenerative disorders [55], joint diseases [56], cardiovascular diseases [57], autoimmune diseases [58], and blistering skin diseases [59], etc. Based on stem cells' capacity to divide indefinitely and their functional differentiation into any type of tissue, the discovery of stem cells has offered a potential treatment for many incurable degenerative diseases, restoring organ function [60-64]. However, current stem cell therapies face limitations such as limited stem cell sources, extreme time consumption for autologous cell therapy, immune rejection upon allogeneic transplantation, ethical issues concerning embryonic stem cell (ESC) application, tumor formation, and "epigenetic defects," necessitating new strategies [65-72]. Allogeneic induced pluripotent stem cells (iPSCs) have been used for disease treatment, but their prolonged somatic cell reprogramming and tumor formation make them challenging for stem cell-based therapies [73, 74]. Furthermore, extended use of immunosuppressive medications in allogeneic iPSC therapy has a greater tendency to cause many side effects [75, 76].

Tissue regeneration gives rise to new tissues in order to restore damaged tissues' function [77-79]. CSCs, similar to iPSCs, retain characteristics essential for tissue regeneration such as high capability for self-renewal, "pluripotency," differentiation potential, and a high level of proliferation [80-88]. Interestingly, new connections have been discovered between iPSC generation and tumor cell plasticity [89]. However, the low efficiency of cancer cell reprogramming with pluripotent factors limits the use of "cancer-iPSCs" in stem cell-based therapies [90, 91].

Extracellular matrix (ECM) provides a convenient environment that supports cell expansion and tissue formation [92, 93]. 3D scaffolds enable rapid tissue repair using an artificial ECM environment [94, 95]. 3D culture methods vary based on whether they include scaffolds or not [96]. Effective 3D cell scaffold methods for enriching CSCs are needed due to limitations in existing methods [97].

The unique properties of CSCs, including self-renewal, pluripotency, immune modulation, and the ability to differentiate into heterogeneous lineages of cancer cells, offer novel strategies for the application of allogeneic CSCs to a large population for disease modeling, drug discovery, and the revolution of economically viable stem cell-based therapy, which could significantly reduce immune rejection. However, further clinical studies are required to ensure efficient effects *in vitro* and *in vivo*. In fact, normalization of CSC differentiation can be activated in the future to treat multiple incurable degenerative diseases.

II. CANCER STEM CELLS ARE QUALIFIED STEM CELL CANDIDATES FOR TISSUE REGENERATION

Tissue regeneration gives rise to new tissues in order to restore damaged tissues' function [98, 99]. The high proliferative and differentiation capacities of stem cells are crucial for treating various incurable degenerative diseases and injuries through differentiation into mature cells [100-102]. Scientists are investigating novel ways to improve stem cell therapy for tissue regeneration [103]. Tissue regeneration and "tumorigenesis" have common characteristics that differ slightly, whereas tissue regeneration is misused by cancer cells [104].

Self-renewal involves stem cells dividing to produce daughter cells with identical prospects of development, enabling excellent replication while maintaining vast developmental and replicative capacity [105]. Stem cell self-renewal is crucial for effective tissue regeneration [106]. Stem cells

replicate and give rise to duplicate cells of the original cells [107]. The self-renewal and differentiation of stem cells are determined by signals received from stem cell niches [108-110]. Similar to normal stem cells, the CSC niche governs the self-renewal and differentiation properties of CSCs [111]. Optimized self-renewal in cancer stem cells is crucial for effective cell development, similar to tissue regeneration [112].

Many tumor CSCs retain pluripotency, the ability of individual cells to differentiate into all cell types of the adult human body, regulated by the core transcriptional factors octamer-binding transcription factor 4 (OCT4), sex-determining region Y-box 2 (SOX2), and homeobox protein NANOG (NANOG) [113-117]. Human pluripotent stem cells, such as ESCs and iPSCs, can differentiate into all cell types, providing unprecedented opportunities for cell therapies for the treatment of incurable degenerative diseases and injuries [118, 119]. ESCs harvested from pre-implantation embryos have the potential to differentiate into any cell type derived from the three germ layers of ectoderm, mesoderm, and endoderm [120-122]. Furthermore, iPSCs can be generated from various differentiated cell types through the expression of a set of defined transcription factors [123]. In 2006, Takahashi and Yamanaka discovered that somatic cells could be reprogrammed into a pluripotent state involving four transcription factors, OCT4, SOX2, c-MYC, and Krüppel-like factor 4 (KLF4), and that these reprogrammed iPSCs were similar to human ESCs [124-126]. Tumorigenesis exhibit similarities between embryonic development and the ability of ESCs, and CSCs to differentiate into heterogeneous lineages of cells [127]. Cancer maturation involves proliferation through transformed protein expression and signaling pathways, promoting the survival and proliferation of premature CSCs [128-131]. Thus, pluripotent stem cells such as ESCs, iPSCs, and CSCs share similarities between self-renewal, tumor formation, rapid proliferation, and cellular plasticity [132-135].

Stem cell plasticity involves cells' ability to flexibly change their characteristics, which is essential for tissue regeneration and the differentiation of stem cells, whereas CSC plasticity is regulated by tumor microenvironmental signals, playing a crucial role in therapeutic resistance, tumor relapse, and metastasis [136-141]. Hence, modulating cell plasticity in order to obtain differentiated cells of interest has caught the attention of scientists [142, 143].

Epithelial-to-mesenchymal transition (EMT) is a genetic process involving epithelial cells transforming into mesenchymal phenotypes, impacting embryonic development, tissue regeneration, tumor progression, and therapy resistance, resulting in invasion and metastasis of tumors [144-147]. iPSC generation from somatic cells involves mesenchymal-to-epithelial transition, the reverted process of EMT [148, 149]. Evidence suggests cancer cells retain tumor-initiating potential due to their plasticity modulation, which supports EMT mechanisms [150]. Clinical studies show that EMT is associated with tissue regeneration in several tissue models [151, 152]. Hence, there is a tangential connection between tissue regeneration and tumorigenesis [153].

Ensuring cells thrive in a conducive environment with cells, scaffolds, and growth factors for proliferation and differentiation is vital to tissue regeneration [154-158]. Repair of injured tissue involves the production of extracellular matrix components, which are restored over time to mimic normal tissue, modulating the cellular processes for tissue reconstruction [159]. ECM signals cells, regulating proliferation, migration, and differentiation; thus, tissue formation and regeneration heavily rely on cellular interaction with ECM [160]. Extracellular matrix scaffolds promote tissue-specific remodeling and repair in various organs, fostering a regenerative microenvironment and functional reconstruction [161-163]. 3D culture methods vary based on whether they include scaffolds or not [164, 165]. 3D scaffolds enable rapid tissue repair using an artificial ECM environment [166].

A precise *in vitro* and *in vivo* demonstration of tissue of interest is under development based on 3D culture models in order to imitate extracellular matrix and provide an appropriate niche for CSC enrichment in various cancer cell lines, such as cholangiocarcinoma [167], lung carcinoma [168], colorectal cancer [169], acute myeloid leukemia [170], glioblastoma [171], hepatocellular carcinoma

[172], melanoma [173], breast [174], prostate [175], neuroblastoma [176], ovarian cancer [177], etc. 3D culture models are more favorable than two-dimensional culture models, but due to variations in "biomaterials," "manufacturing methods," and tumor heterogeneity, the development of a common 3D culture model demonstrating all tumor niches is uncertain [178-180]. And also, it is crucial to advance current knowledge about various tumor differentiation mechanisms [181, 182].

III. NORMAL CELL DIFFERENTIATION POTENTIAL OF CANCER STEM CELLS

Differentiation therapy offers promising cancer treatment for malignant cells with tumorigenicity reduction rather than cytotoxic lysis [183]. CSCs are naturally capable of differentiation into heterogenous lineages of tumor cells and progress through a decreased ability to differentiate into a normal cell state [184].

Differentiation therapy induces cancer cells to differentiate into benign or normal cells [185, 186]. CSC differentiation therapy involves tumorigenic CSC differentiation into low-tumorigenic stem cells or mature cells, reducing the “CSC pool” for cancer eradication [187, 188].

Solid tumor differentiation is induced by differentiation inducers both *in vitro* and *in vivo* [189]. Currently, leukemia treatment is mainly focused on leukemic cell differentiation with various differentiation inducers [190]. All trans-retinoic acid induces differentiation, which transforms acute promyelocytic leukemia into mature granulocytes [191]. Melanoma cells have the capacity to differentiate into "mesenchymal lineages" [192]. Differentiation therapy for liver cancer involves altering hepatocyte dedifferentiation and promoting tumor differentiation into normal liver cells [193]. Redifferentiation of nodule hepatocytes gives rise to normal liver characteristics [194]. Neuroblastoma cells differentiate into normal adult neuronal cells under specific growth conditions [195-197]. Interleukin-15 gives rise to normal epithelial differentiation of renal CSCs *in vitro* [198]. Induced differentiation of osteosarcoma-initiating cells gives rise to adipocytes, restraining tumorigenicity [199]. All trans-retinoic acid promotes osteogenic differentiation in osteosarcoma cells [200]. Induced differentiation of hepatocellular carcinoma cells generates normal hepatocyte-like cells [201]. Breast cancer cells undergo transdifferentiation, generating adipocytes both *in vitro* and *in vivo* [202]. Polyphenols, derived from plants, have potential therapeutic applications in anti-cancer therapies due to their reduced side effects and antioxidant properties, as well as their targeting of signaling pathways regulating cellular processes such as proliferation, apoptosis, and differentiation [203, 204].

Thus, CSCs have the potential to produce new tissues upon induced differentiation without reprogramming pluripotent factors *in vitro* or *in vivo,* which in turn promotes tissue regeneration. Transdifferentiation and dedifferentiation of tumor cells, or redifferentiation of CSCs into normal adult cells, exhibit potential connections with tissue regeneration [205, 206]. Lacking information about stem cell niche pathways controlling cellular quiescence and self-renewal in normal stem cells and CSCs is considered a major hurdle that could potentially hinder the application of the CSC differentiation therapy concept to stem cell-based therapies [207]. Understanding the CSC differentiation mechanisms of solid tumors will advance stem cell-based therapies in the future.

IV. UNSHAKABLE IMMUNE CONTROL OF CANCER STEM CELLS

“Immune privilege” offers shelter to vital tissues against foreign antigens [208]. CSCs develop defense mechanisms against immune detection and destruction using immune modulation strategies that enable them to bypass innate and adaptive immune control [209-211]. CSC immunological functions include evasion from immune clearance, induction of "tumor-antigen-specific T cells," activation of regulatory immune cells, and release of immune suppressive molecules in the tumor microenvironment [212-215].

Classical major histocompatibility complex (MHC) genes encode glycoproteins crucial to the immune response [216-218]. Human leukocyte antigen (HLA) genes are highly polymorphic in the human genome [219, 220]. MHC molecules recognize T cell and NK cell receptors [221-224].

In many solid tumors, CSCs show low expression of MHC-I and II [225-227]. During embryonic development, ESCs either express MHC-I at a low level or have no MHC-II expression at all, making them poor targets for the mother's immune cells [228, 229]. Similarly, downregulation of MHC-I expression in various CSCs makes them resistant to immune detection, evading T cells and NK cell killing [230-232]. Many tumor CSCs maintain restricted MHC-I levels to avoid NK cell recognition [233, 234].

HLA-G is a nonclassical HLA class-I molecule expressed in placental trophoblasts and CSCs [235, 236]. Tumor cells use *HLA-G* expression to bypass immune detection in the host [237, 238]. CSCs upregulate MHC class 1 or Human Leukocyte Antigen-G (*HLA-G*) expression to inhibit NK cell activation [239, 240].

Core tumor-associated cells in TME involve neutrophils [241], macrophages [242], regulatory T cells [243], and myeloid suppressor cells [244], creating an immunosuppressive environment for growth. Tumor cells use various mechanisms to bypass NK-mediated immune destruction [245]. Tumor microenvironments downregulate natural killer group 2, member D receptor ligands, causing tumors to escape immune detection [246-248]. Limited NK cell infiltration limits tumor elimination. NK cells can also be excluded from TME [249]. Defects in dentritic cell maturation, which are crucial in immune responses, lead to tumor progression [250, 251]. Tumor-associated macrophages play a crucial role in innate immune responses and in the likelihood of tumor formation, and this immunosuppressive environment can weaken T-cells and promote tumor development using various strategies [252-255]. Myeloid-derived suppressor cell accumulation is promoted by various stress conditions that weaken immature myeloid cell differentiation, suppressing "antitumor immune responses" in order to maintain the CSC population [256-258]. Neutrophils contribute to tumor progression both directly and indirectly by influencing the tumor microenvironment and inducing tumor progression by producing cytokines, chemokines, reactive oxygen species, proteinases, and toxins that are able to alter the tumor microenvironment [259-264]. In many solid tumors, regulatory T cells and regulatory B cells facilitate tumor development via several immunosuppressive mechanisms [265-271].

Concerning these basic immunomodulatory mechanisms, CSCs are tricky players to escape immune detection and survive within a foreign host, which is a fundamental requirement in allogeneic stem cell treatments.

V. DISCUSSION

A stem cell bank stores donor stem cells prior to clinical application [272, 273]. The generation of MHC/HLA-matched allogeneic stem cell banks for a large population could significantly reduce immunological rejection and the cost of stem cell-based cell therapy [274].

Although autologous methods offer a reduced risk of immunological rejection compared to allogeneic donor methods [275, 276], autologous transplantation is costly and requires a lengthy process, limiting its therapeutic potential [277]. There is no need to identify a HLA-matched donor in autologous transplantation, but due to several shortcomings, allogeneic stem cell banks are critical to improving their therapeutic efficacy, and it is crucial to identify a HLA-matched donor in order to prevent immune rejection upon allogeneic transplantation [278, 279]. Allogeneic treatments offer viable manufacturing of multiple "allografts" from a single donor, simplifying the stem cell manufacturing process and reducing the time to transplant stem cells to patients [75]. However, allogeneic stem cell therapy is limited to HLA-matched donors [280].

CSCs resemble iPSC characteristics, potentially allowing reprogramming in order to generate an infinite CSC pool, but cancer cell reprogramming faces many challenges due to the negative association of cancer cell diversity with successful reprogramming [281, 282]. Furthermore, cells reprogrammed with pluripotent factors have a high potential for tumor formation [312].

CSCs possess immune privilege, enabling them to bypass immune control within the host by developing immune modulation strategies against immune responses [283, 284].

Presently, cancer therapy considers eradicating cancer via differentiation of CSCs rather than killing

them through cytotoxicity [285-287]. Cancers such as leukemia [288, 289], glioma [290], liver [291], colon [292], breast [293], skin [237], ovarian [294], lung carcinoma [295], neuroblastoma [296], and melanoma [297], etc. offer positive results to differentiation therapy. For instance, successful application of polyphenols manifests differentiation in many tumors [298, 299]. Resveratrol exhibits antitumor effects in various cancers, modulating tumorigenesis [300, 301] and inducing the differentiation of glioma stem cells into non-tumorigenic cells, potentially eliminating tumors [302]. Flavonoids are plant compounds with therapeutic effects on glioma cells, increasing differentiation biomarkers and preventing cancer [303]. Chlorogenic acid induces the differentiation of neuroblastoma cells *in vitro* and *in vivo* by inhibiting acetyl-CoA acetyltransferase [304]. Kaempferol and melatonin promote neuroblastoma differentiation [305]. However, incomprehensible details on normal differentiation pathway mechanisms need to be resolved by researchers [189].

Generation of the desired CSC line of interest *in vitro* and *in vivo* is viable [306, 307]. However, isolation and *in vitro* and *in vivo* replication of CSCs are limited due to the lack of CSC model development [308, 309]. Furthermore, limitations in *in vitro* and *in vivo* two-dimensional cultures of CSC restrict CSC-based clinical studies [310, 311]. Interestingly, 3D cellular scaffolding models offer a pragmatic tumor microenvironment, which is crucial for tissue regeneration [312, 313]. 3D tumor models enable *in vitro* and *in vivo* CSC replication, enabling CSCs to generate unlimited stem cells for stem cell-based therapy [314, 315]. Effective 3D cell scaffold methods for enriching CSCs are needed due to limitations in existing methods [316, 317]. Thus, standardized 3D tumor models could revolutionize *in vitro* and *in vivo* replication and expansion of CSCs in preclinical settings [318, 319].

VI. CONCLUSION

In conclusion, immune modulation of CSCs prevents the elimination of CSCs by the immune system, enabling allogeneic CSCs for various clinical studies. The unique properties of CSCs, including self-renewal, pluripotency, immune modulation, and the ability to differentiate into heterogeneous lineages of cancer cells, offer novel strategies for the application of MHC/HLA-matched allogeneic cancer stem cells to a large population for tissue regeneration, disease modeling, drug discovery, and the revolution of economically viable stem cell-based therapy, which could significantly reduce immune rejection. However, further clinical studies are required to ensure safe and efficient effects *in vivo*. The use of allogeneic CSC for the regeneration of incurable degenerative diseases based on differentiation therapy may be an alternative to iPSC technology. Therefore, CSC may represent a more promising stem cell candidate in stem cell-based therapy, and I believe that CSC will be one of the stem cell researchers' great interests, improving patient outcomes.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

AUTHOR CONTRIBUTIONS

JJA contributed to the conception and design of the study and wrote sections of the manuscript.

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