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Updates of Role of Stem Cells in Cancer Therapy

Literature Review

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Abstract – Stem cell- based treatments show significant remedial potential for treating different human diseases, including cancer. Among the cell types that can be utilized for this reason, mesenchymal stem cells (MSCs) are considered as promising source of stem cells in customized cell-based treatments. The innate tumour-tropic property of MSCs can be utilized to target cancer cells. Albeit the effects of MSCs on cancer progression stay tricky, they have been genetically adjusted or designed as targeted anticancer agents which could hinder tumour growth by impeding various processes of cancer. Also, there are close interactions among MSCs and cancer stem cells (CSCs). MSCs can direct the growth of CSCs through paracrine mechanisms. This review aims to focus on the current information's about MSCs-based tumour treatments, the opportunities and difficulties, as well as the forthcoming of its further clinical implications.

Keywords – Cancer stem cells, Embryonic stem cells, Cancer therapy.

INTRODUCTION

MSCs are non-hematopoietic cells that were first found in bone marrow and detailed around a long time back by Friedenstein and his colleagues [1, 2]. Studies have shown that MSCs exist in various tissues. To date, MSCs have been effectively isolated from different organs including brain, liver, lung, kidney, muscle, thymus, pancreas, skin, bone marrow fat tissue, foetal tissues, and umbilical cord [3]. Likewise, MSCs are known as multipotent cells which can differentiated into adipocytes, myocytes, osteocytes, and chondrocytes [4-6]. In 2006, the International Society for Cellular Therapy proposed three minimal criteria to characterize human MSCs. They should express CD105, CD90, and CD73 and lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR surface molecules. Also, they should stick to plastic in culture and differentiate into osteocytes, chondrocytes, and adipocytes [7]. Also, MSCs have exceptional immune-phenotypic capacity, tissue-repair capacity, and immune-regulatory capacity [8]. In this way, attributable to their overall immune evasiveness and general immune dampening activities, MSCs can be used in an allogenic setting and are promising seed cells for cell treatment and tissue engineering [9]. Additionally, different preclinical preliminaries recommend that MSCs show extraordinary potential for cancer treatment, despite the fact that obstacles and risks were described [10].

Studies have shown that MSCs are fit for migrating directionally to specific tissues, which is named as homing. The tropism property of MSCs into sites of injury and cancer makes them ideal vehicles for targeted tumour treatment, albeit the specific mechanism of MSCs homing isn't totally understood. Continuous preclinical preliminaries recommend that MSCs are reasonable targets for cell treatment in various cancers. In any case, the antitumor impacts of MSCs are as yet dubious. In different types of cancer, some studies make shown proliferative impacts, while others exhibit inhibitory impacts of MSCs on tumours [11]. For example, MSCs have tumoricidal effects on liver, lung cancer cell lines, and pancreatic cancers in vitro and in vivo [12-14]. In contrary, it has been shown that MSCs are fit for improving movement and metastasis of kinds of growth, for example, breast

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disease and colon cancer [15-18]. What's more, MSCs might apply therapeutic function through an immune evasive mechanism, which will shield MSCs from immune detection and prolong their persistence in vivo [9]. Besides, the endurance of MSCs in the tumour and bio distribution of MSCs ought to take more consideration while planning a preliminary, which might impact the results of study. For instance, albeit human MSCs were found by staining in the tumours 1 day after IV infusion in a mice model, the cells nearly were cleared following one week [19]. Notwithstanding, even following 11 weeks MSCs were as yet seen in the tumor, in spite of the fact that at extremely low numbers [19]. In an in vivo study of colon cancer, exogenous MSCs were as yet ready to control immune reaction of the cancer microenvironment even 1 year after the last MSCs injection [20]. In this review, we sum up ongoing advances of MSCs in the therapy of cancer and insights into potential strategies for cancer therapy.

I. MSCS AND CANCER

1.1 Disparity in Impacts of MSCs on Tumour Progression

Extensive studies have been performed to investigate impacts of MSCs on cancer in late years. Be that as it may, this issue is still under debate. Controversial outcomes have been accounted for. Several studies have shown that MSCs advance tumour progression and metastasis through impacting signalling pathway [18, 39], while different studies propose that MSCs influence the pathways that can suppress both proliferation and apoptosis [13, 40].

Researches have exhibited that MSCs would be recruited into cancer sites, advancing tumour growth, and angiogenesis through differentiating into cancer associated myofibroblasts and secretion of proangiogenic cytokines (e.g., interleukin (IL)- 6, vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGF-β) [21-23]. In the meantime, the recruited MSCs likewise enhanced cancer metastasis through expanding lysyl oxidase [24]. Another tumour advancing impact of MSCs is ascribed to their protection for breast cancer cells from immune clearance through modulating regulatory T cells and restraining natural killer (NK) cells and cytotoxic T lymphocyte (CTL) functions [25]. Moreover, MSCs have been found to form cancer stem cell niche in which tumour cells can preserve the possibility to proliferate and support the malignant process [41]. Additionally, expanding evidences recommend that MSCs advance cancer angiogenesis through their capability to differentiate into pericytes or endothelial-like cells as well as by their secretion of trophic factors and cytokines, proangiogenic factors, plasminogen activator, and growth factors [42, 43]. Hence, MSCs advance tumour growth and metastasis through stimulation of angiogenesis, cancer stem cell niche maintenance, and immune protection. Besides, it has likewise been demonstrated the way that MSCs can influence tumour development and progression through miRNAs. In a xenograft tumour model, researchers exhibited that human umbilical cord MSCs (hUCMSCs) capably advance the growth of lung adenocarcinoma (LUAD) cancer cells by transferring miR-410. The findings recommend that modifications of hUCMSC-determined extracellular vesicles (hUCMSC-EVs) might be a promising therapeutic choice for treatment of cancer [44]. In a mice model, study found that gastric cancer tissue-derived MSCs can essentially advance HGC-27 growth and migration by means of expanding the expression of miR-221, which might be as a novel biomarker in gastric cancer [45].

Conversely, it has been shown that the unmodified MSCs have antitumor impacts both in vitro and in various animal models of cancer, which is credited to the factors emitted by MSCs that can supress the proliferation of glioma, melanoma, hepatoma, and breast cancer cells [46-48]. Studies have demonstrated that MSCs display antiglioma impact through inhibiting vascular growth in glioma cells, which is mediated by the downregulation of platelet-derived growth factor (PDGF)/PDGFR axis [28]. Additionally, human umbilical cord derived MSCs (hUC-MSCs) have been displayed to inhibit growth of breast cancer by initiating cancer cells death and suppressing angiogenesis [29]. Another review detailed that human bone marrow-derived MSCs display the possibility to suppress the growth of breast cancer and inhibit lung metastasis by decreasing their proliferative ability [30]. Moreover, MSCs have been displayed to have antiangiogenic impact both in vitro and in vivo [49]. MSCs likewise can inhibit cancer growth in an exceptionally inflammatory and angiogenic Kaposi's sarcoma model [50]. Both in vitro and in vivo studies have shown that MSCs derived from foetal skin can inhibit the growth of human hepatocellular carcinoma (HCC) cells and can lessen cell proliferation, colony formation, and expression of oncogenes [48].

II. INHIBITORY IMPACT OF MSCS ON TUMORS

2.1 MSCs, Cancer Stem Cells and Cancer Microenvironment

Cancer stays as one of the most difficult diseases in spite of extensive studies have been performed and novel systemic treatment advances during late years. Specifically, when cancer is diagnosed to have metastasized, therapies are considerably less

successful; while it can frequently be treated successfully by surgery or local irradiation before it has spread [51]. Consequently, it is fundamental and basic to understand the biological processes behind the progression of cancer cells towards metastasis. Cancer cells in primary cancers reside in a complex microenvironment containing various cell types, including endothelial cells of blood vessels, lymphatic circulation, fibroblasts, and various bone marrow-derived cells, like macrophages and MSCs. It has been legitimate that cancer cells secret chemokines, cytokines, and growth factors recruiting MSCs into the tumour sites. Thusly, MSCs, as a part of tumor microenvironment, influence growth development and metastasis through emission of cytokines and chemokines [52, 53]. Hence, the process of growth progression has been viewed because of a developing crosstalk between various cell types inside the cancer and its encompassing host tissue and organ or growth stroma [54].

Cancer stem cells (CSCs), which have chemotherapy resistance, have been considered as the base of tumours and can resist chemotherapy, making sense of cancer recurrence even many years after treatment is finished. The proof that CSCs specifically oppose treatment is given by a multitude of observations in cell culture, animal models, and cancer patients. For instance, direct investigation of apoptosis during cell culture showed that differentiated colon cancer cells are initiated to die after chemotherapy, while CSCs from a similar culture survive after toxic damage. Additionally, these enduring CSCs can ready re-establish the culture, showing that they are responsible for treatment failure [55]. Chemotherapy-resistant CD133+ CSCs were likewise seen in lung and liver cancer [56, 57]. Essentially, the peculiarity of CSCs escape from treatment was likewise seen in xenograft studies. Chemotherapy treatment of xenotransplanted CSCs prompts an increase in CD133+ CSCs in the cancer [58]. This showed that CD133+ CSCs are more resistant to chemotherapy drugs in vivo contrasted with differentiated CD133+ cells. What's more, breast CSCs and GBM CSCs isolated from patient specimens have showed selective resistance for different chemotherapies [59, 60].

Besides, different studies have shown that the tumour stroma assumes significant roles in the survival, growth, and metastatic progression of cancer. In the hypoxic environment, the tumour stroma can expand its secretion of signalling proteins, for example, tumour necrotic factor-α (TNF-α), TGF-β, PDGF, and hepatocyte growth factor (HGF) [61]. In the meantime, tumour oxygenation status is firmly connected with its aggressive behaviour. Experimental solid tumours contain a critical part of microregions that are constantly or momentarily hypoxic. Hypoxia assumes critical roles in tumour progression including cancer angiogenesis, mutation rate, metastasis and resistance from radiation and chemotherapy [62]. Numerous molecular pathways have been shown to mediate these hypoxia-induced reactions in tumours. Among them, hypoxia-inducible factor-1 (HIF-1) is a key signalling pathway regulatory tumour responses to hypoxia [63]. Momentarily hypoxic microenvironment in solid tumour might represent the stem cell niche somewhat, in which HIF-1α stabilization and activation of stromal-cell determined factor-1 (SDF1), VEGF, and Chemokine (C-X-C theme) Receptor 4 (CXCR4) occur, attracting MSCs homing and recruitment subsequently [64, 65]. Besides, the state of tumour-induced hypoxia, which frequently propagates the inflammatory state, prompts the secretion of various growth factors (e.g., endothelial development factor-A, and fibroblast growth factor), in this way activating MSCs recruitment and tumour growth through stimulation of growth angiogenesis [23, 66].

III. MSCs and Antitumor Therapy

3.1 MSCs-Derived Exosomes as Vehicles for Antitumor Therapy

Exosomes are nano-sized (<100 nm) and lipid-bilayer-encased extracellular vesicles that are conveyed by many types of cells. They are found to play a critical role in intercellular communication through the exchange of genetic molecules like mRNA and microRNAs, as well as proteins [67]. A common characteristic of human cancers is the aberrant expressions of either oncogenes, oncomiRs, or tumour suppressors. The MSCs-derived exosomes which contain a variety of miRNAs can be taken up by cancer cells and function in them. For example, miR-100 has been seen as downregulated in all subtypes of breast cancer, including the luminal A, luminal B, basal-like, and human epidermal growth factor receptor 2 (HER2) subtypes [34]. It is improved in MSCs-derived exosomes and could suppress in vitro angiogenesis through modulating the mTOR/HIF-1α/VEGF signalling axis in breast cancer cells [35].

Anyway, studies with controversial outcomes on MSC-derived exosomes in tumour progression have been represented, including promoted influences [36-38] and suppressive effects [68, 69]. The controversy effects of MSCs-derived exosomes may result from different tissue-derived MSCs used and different components of exosomes applied, various protocols applied for exosome collection, as well as different cancer model and stages of cancer considered. Similarly, there is also another issue that the exosomes secreted by MSCs are not created equivalent.

Hence, comprehensive studies are supposed to advance our knowledge and concerns about cancer research and treatment using MSCs-derived exosomes. One expected approach for clinical application of MSCs-derived exosomes for cancer therapy is that MSCs should be genetically engineered for stable expression of some cancer killing genes before the isolation of exosomes from MSCs, similarly as Sueon Kim et al. declared for generating antigen-explicit CD8+ T cells for adoptive cell therapies against viral infection and tumours [70].

MSCs have the characteristics of tumor tendency and avoidance of immune clearance; subsequently, it is promising that MSCs are used as vehicles to convey anticancer therapies [71]. It has been shown in various preclinical in vitro migration experiments and in different tumours models, for example, hepatoma [72], leukaemia cells [73], breast cancer [52], and osteosarcoma [74]. It could be a suitable methodology that MSCs conveying anticancer drugs designated therapy of tumours. For example, Bonomi et al. seen that MSCs-Paclitaxel (PTX) inhibit the proliferation of human myeloma cells in vitro 3D dynamic culture system [75]. The anticancer impact of MSCs-PTX has likewise been displayed on pancreatic carcinoma cells in vitro [76]. MSCs are additionally encouraging apparatus for cisplatin (CDDP) conveyance towards the cancer [71]. What's more, researches have shown that MSCs with suicide genes or apoptotic genes targeting for cancer is a promising methodology. In vivo and in vitro studies have shown that the expression of interferon-γ in MSCs transfected by adenovirus can successfully kill glioma cells [77]. It is important that in a model of lung metastasis of prostate malignant growth, MSCs expressing IFN-β could prolong the survival period, and its mechanism is that IFN-β could promote cancer cell apoptosis, inhibit angiogenesis, and increment the activity of natural killer cells [78]. Similarly, adenovirus-transfected MSCs expressing interferon-γ hinder proliferation of leukaemia cells and prompt apoptosis of leukaemia cells in vitro [79]. In models of lung metastatic carcinoma, a study has discovered that MSCs conveying TNF-related apoptosis-prompting ligand (TRAIL) diminish cancer growth and recurrence and inhibit the growth of lung metastatic foci in most mice [80]. Study has announced that in glioma mice, cancer tropism of umbilical cord MSCs carrying TRAIL was improved after irradiation and its proapoptotic impact on growth cells was enhanced by MSCs-TRAIL [81]. What's more, the previous studies likewise have shown the way that MSCs could be genetically changed with herpes simplex infection thymidine kinase (HSV-TK), and the cancer cells could be killed by HSV-TK/GCV suicide gene treatment [82-84]. A new report showed that histone deacetylase inhibitors (HDACis) prompted apoptosis of chemo-resistant cells really, as CD123/CD47-positive cells, which were found as perhaps filling in as a vital role for chemo-resistance in tumour microenvironment. Moreover, HDACis productively focused on and eliminated chemo-resistant leukaemia blasts in a xenograft AML mouse model [85].

The immune system plays a significant role in monitoring the growth of malignant cells. Hence, stimulating the body's own immune system for antitumor treatment is a profoundly encouraging strategy. Interleukins (ILs) are cytokines that regulate inflammation and immune reaction and have been displayed to show antitumor impacts through direct tumour killing or active regulation of the endogenous immune system [86]. MSCs have been used to convey interleukins that can improve the anticancer immune surveillance by activating NK cells and cytotoxic lymphocytes [86]. For example, the IL-18 secreted MSCs were corresponding with enhanced T cell infiltration and antitumor immunity in mice bearing non-invasive and painless gliomas [87]. Essentially, MSCs engineered to express IL-12 prevented metastasis into the lymph nodes and other internal organs along with expanded cancer cell apoptosis in mice bearing pre-established metastases of melanoma, breast, and hepatoma tumors [88]. Likewise, MSCs engineered to express IL-12 was tried in various mouse tumors models of melanoma and glioma [46]. Other immune stimulatory molecules, as CX3C chemokine fractalkine (CX3CL), have additionally been engineered in MSCs. CX3CL1 is known as strong Tcell for a cell chemo-attractant. Recent studies uncover that CX3CL1 is a driver of T cell migration to the omentum in esophago-gastric adenocarcinoma (EAC). Previous research has shown that injection of an adenoviral vector expressing CX3CL1 can induce strong antitumor immune reactions by activating both NK cells and T cells [89]. Likewise, intravenous or intra-tracheal conveyance of MSCs-CX3CL1, activating T cells and NK cells, was seen to firmly inhibit process of lung metastasis and increase survival of mice carrying lung metastases cells [90, 91]. Taken together, the tumour trophic homing capacity makes MSCs ideal cell conveyance vehicles for personalised cell-based targeted-cancer gene treatment.

3.2 Inhibition of Migration for Antitumor Therapy

Tumour has been seen as a "wound that never heal" which enlists MSCs in its microenvironment through production of paracrine and endocrine signals. So hypothetically, inhibition of MSCs homing will prevent the growth of tumour. For example, PDGF receptor β (PDGFRβ) has been accounted to assume a significant role in recruitment of MSCs towards tumour sites [92]. Furthermore, Simona Camorani et al. have exhibited that interfere with the PDGFRβ-mediated crosstalk between BM-MSCs and tumour cells using a nuclease-resistant RNA aptamer could inhibit the migration of MSCs towards tumour cells and hampering

tumour aggressiveness [93]. The classic signalling administering MSCs homing is SDF1-CXCR4 axis. SDF1 is profoundly expressed in active multiple myeloma, as well as in bone marrow sites of tumour metastasis, killing SDF1 with a high-affinity L-RNA Spiegelmer to SDF-1 has been exhibited to decrease the cancer progression [94]. In tumour biology, various studies observed the prerequisite of Akt and Wnt signaling for the migration, invasion, and survival of tumor cells [95-97]. Recent studies have shown that MSCs are involved in mediating these signalling pathways to impact migration of tumours. In glioma cells and mice tumours, upregulation of PTEN by hUCBSC downregulated Akt and (phosphoinositide 3-kinase) PI3K flagging pathway brings about the restraint of relocation [98]. Likewise, consequences of a study exhibited that overexpression of HNF4α suppresses HCC progression by reducing hepatoma cell growth and metastasis through downregulating the Wnt/β-catenin signalling pathway [99].

IV. Malignant growth Resistance

CSCs and the Tumour Microenvironment The study of TME stays a place of prime interest and importance in solid tumours because of TME's significant role, which might tumour resistance and progression. It has been isolated into various parts, apparent by histopathological analysis, where the connection among normal and tumour tissue appear to predominate [100-102]. Other than various tumour compositions, the cross-over in signalling pathways and cell interactions can produce a significant phenotypic collection within niches and CSCs that is more complex when the tumour is more aggressive. CSCs show different transcriptional and epigenetic marks to keep up with the niches [103-111]. CSCs can construct an extensive solid network of connections between the tumour and the normal tissue, characterizing a specific role for each niche, easily connected by their dependence relationships. A specific niche normally develops under hypoxic conditions, which is the genuine driver for mediators of stemness [112]. CSCs can endure on account of their high metabolism to burn calories and affinity with nutrients, for example, glucose, which promotes migration and scattering of the tumour, inciting hypoxia and necrosis [112,113]. In addition, CSCs prompt the synthesis of angiogenetic factors and the formation of new vessels [114], and they are upheld by the structures and signals coming from normal tissue, for example, the CAF and niche ECM [115-118]. One more fascinating aspect that should be researched is the connection and interaction between immune cells and CSCs in the likely advancement of new medicines that explicitly target CSCs and immunity. Masciale et al. distinguished and isolated CSCs based on ALDH activity, and analysed the tumour infiltrating T-lymphocytes (TILs) of non-small cell lung cancer (NSLC) patients to notice the relationship among CSCs and TILs. Data from 12 patients showed a positive relationship among CSCs and CD3+ cells and a stronger correlation among CSCs and cytotoxic CD8+ T-lymphocytes, consequently proposing a close interaction between the two cell populations [119].

These data show that CD8+ T cells could be vital for a cell-mediated anti-tumour response by means of T-cell receptors restricting with CSCs' antigen. Disentangling these experimental information, a potential clarification for the positive correlation among CSCs and cytotoxic CD8+ T cells might be that the CSCs stimulate the immune system, triggering an immune reaction, especially the CD8+ T cells, to suppress CSCs [119]. Understanding intricate interaction between T-lymphocytes and CSCs within the tumour would assist develop novel combined treatment approaches. These could optimize the clinical benefit of current immunotherapies by interfering with the underlying mechanisms of tumour cell immune evasion [120-123]. Specifically, researchers have recently concentrated completely on the cytokines delivered by immune cells, which appear to induce CSC maintenance and growth [124,125]. These novel discoveries have prompted new approaches, like single-cell genomics, epigenomic technology, and 3D culture systems, which give new opportunities to significant understanding of this interaction [126-129].

CRISPR-Cas9 and RNA interference screening have likewise given new insights into in vivo dependence and niche cell interactions [126,127]. Single-cell sequencing endeavours and multi-regional studies have characterized the compositions of various intra-tumoral cells [129]. Moreover, CSCs' genomic data is utilized to analyse tissue biopsies [130]. The authors distinguished and confined CSCs through fluorescent-activated cell sorting (FACS) to investigate cell conduct in vitro and gene expression from the surgical tumour tissue of 22 NSCLC patients [131]. Several studies isolating CSCs in contrast, defined a model in which individual tumours are made out of various subtypes of cells, suggesting that tumour micro-environmental variety creates cell heterogeneity [114,117]. Accordingly, treatments focusing on a single niche have shown restricted efficacy, since several components in the tumour microenvironment promote therapeutic evasion. The heterogeneity of tumours has been researched seriously, and it seems related with intrinsic and extrinsic pathways [132,133]. It relies upon the biological properties of cells, which can enable the tumour, however the unessential elements get from the microenvironment and cell-to-cell

interactions [134]. In this situation, CSCs plays a role as transformed cells, with the capacity to regenerate themselves, increase resistance to hypoxia for angiogenic stimulation, facilitate immune system, and increment cytokines and growth factor expression [135]. Ongoing studies have shown the way that cancer cells undergo de-differentiation and return to stem cell like traits, self-renewal, growth, progression, and dissemination [136]. In this specific circumstance, the TME is the mainstay of preservation and dissemination of CSCs. The resistance systems activated by CSCs develop tumour preservation and low reaction rate to common oncological therapies. Obviously, our future capacity to target CSCs will improve with how we might interpret the interaction among CSCs and TME [137-140]. The complexity of TME makes it trying to understand its connection with CSCs, since several components contribute synergistically to stimulate and preserve CSCs' growth and subsequent tumour dissemination [141].

The cancer microenvironment supports CSCs. The tumour microenvironment is primary responsible for the regulation of CSC plasticity, activating stemness pathways and promoting immune escape through cytokine delivery and inactivation of the T-lymphocytes, consequently inducing a tumour cell to obtain the CSC phenotype or a mesenchymal stroma cell to complete the epithelial mesenchymal transition towards cancer phenotype. TME prompts the angiogenetic de novo development by means of CSC spread in the blood stream for metastatic dissemination. In vivo study was performed through xenograft models of highly immune compromised NOD-SCID/IL2g-/ - (NSG) mice, in which the growth capacity of CSCs was compromised-immune cell-dependent, particularly B-lymphocytes and natural killers (NKs) [142,143]. The published data show that the absence of immune cells may directly or indirectly impact tumour growth and the presence of cancer initiating cells (CIC) [144,145]. Consequently, an experimental immunocompromised mice model is viewed as a robust method to understand the dependence of CSCs on TME. One of the most pragmatic ways to deal with this relationship is the engraftment of primary cell culture enhanced in CSCs into immunocompromised mice [143].

The utilization of adequate number of CSCs stays a significant viewpoint, similar to a matrix that supports precise implantation of cells in the specific inoculation site. Matrigel is the most involved enriched matrix in experiments [146,147]. The focus ought to be on fibroblasts within TME (tumor microenvironment) representing the "stromal bed" in the central part of the tumor. The stroma represents the essential component of TME.; as it assumes a vital role in reverting differentiated cells to de-differentiated phenotypes, from which the generation of CSCs takes place. In particular, it drives cells' plasticity through critical signal transmission, for example, the Wnt and Notch pathways [148,149]. Another fundamental viewpoint being considered is the role of CAFs within TME.; for the secretion of development elements and cytokines, for example, platelet-determined development factor (PDGF), and vascular endothelial development factor (VEGF), which initiate cancer movements [149-153]. The regulation of an acidic and hypoxic microenvironment is often characterized by two primary oxygen controller, HIF1A and HIF2A. These factors are susceptible to cell pH modifications, as both hypoxia and pH changes might cause the metabolic switch into a more aggressive cancer cell phenotype through the glycolytic process and the induction of EMT. Furthermore, different occasions promote cancer growth supported by CSCs, for example, the overexpression of C-X-C-chemokine receptors and the upregulation of gene expression of Snail and Twist [154]. The two transcription factors Twist and Snail are individuals from a family of EMT controllers, which initiate metastasis by down-regulating E-cadherin. Their expression is likewise related to the β-catenin signaling pathway.

Late studies relate expression of Snail and Twist with the loss of cell adhesion, increased cell migration, and accumulation of β-catenin signalling, which results in expanded aggressiveness reported in, e.g., metastatic ovarian and breast carcinomas [155,156]. Moreover, researchers have distinguished certain genetic and epigenetic factors assuming a critical role in the idea of plasticity. It has recently been proposed that the metabolic re-programming of cancer cells might address another part of cancer that diverts cancer cell status from non-CSC to CSC [157-159]. Intracellular metabolism sets cell proliferation and differentiation [165], and new insights report that CSCs and their differentiated progeny might show different metabolic states [157,161].

CSCs go through oxidative phosphorylation in breast cancer, in spite of the fact that non-CSC cells especially carryout aerobic glycolysis [162]. Notwithstanding, tumours address a combination of cancer and micro environmental cells communicating through a bidirectional metabolic motion, where each part impacts each other in mutual metabolic reprogramming [163]. In this context, CAFs play a metabolic role in reprogramming cancer cells by prompting a reverse Warburg phenotype [162-166]. Tumor dissemination begins without clinical symptoms, permitting the disseminated cells to acquire a dormant state, which appears to reflect the resistance to treatments in advanced stage tumors [167]. Since dormant cells might cause tumor recurrence, quiescence and slow growth are highlights of tissue-residing stem cells, and a pertinent inquiry is whether CSCs might

be the reason for metastatic dissemination [168]. MICs have been as of late shown in solid tumours, like breast cancer, colon cancer, and lung cancer [169-172].

It is interesting that MICs are found in CSC subpopulations [173]. Tumour dissemination needs an environment for the tumour to spread. The supposed "metastatic niche" may address a native stem cell niche of the distant organ with stem cell properties [172-175]. To sum up, the CSCs' niche is an active environment regulated by developmental signalling pathways, i.e., Wnt, Notch, and the chemokine CXCL12, endothelial-mediated paracrine stimulation, ECM components, and the secreted enzymes, i.e., lysyl oxidase (LOX) [176]. Besides, the release of inflammatory components, like cytokines and enzymes, prompts the primary source of the tumour in a "pre-metastatic niche" found in distant organs [177-179]. Notwithstanding, this condition of quiescence got from the tumour dormancy is because of decreased vascularization (representing antigenic dormancy) and high cytotoxic activity in the immune system (immune—mediated dormancy) [180,181]. At long last, tumour cells might drive progression or tumour growth latency, dependent upon the presence of specific factors and cytokines in the surrounding microenvironment [177]. Specifically, the mutations held onto by these cells keep up with the integrity of the growth [182], and it is presently accepted that TME plays a significant role in forcing the genetic evolution toward certain mutations favourable for cancer cell survival. Among other factors, TME is a promotor of the "clonal" choice that chooses those cells to induce tumor development and maintenance. It is presently well established that CSCs and TME dynamically interact to impact one another, including different cellular players [183-186].

V. The Molecular Mechanisms Switching On Cscs And Metastasis

The hypothesis of cell fusion among macrophages and tumour cells was viewed as the main basic reason for metastasis. From that point forward, different studies have given proof that cell fusion could prompt tumours and their metastasis [187]. The cell fusion cycle might bring about two types of hybrids, heterokaryons or synkaryons. In heterokaryons, the genetic information of the parental cells stays situated in segregated nuclei, accordingly prompting the development of bi-or multi-nucleated hybrids. This was first seen in vitro in the Sendai virus in murine Erlich ascites cells joined with human HeLa as the fusion cells [188]. Changes in the morphological characteristics of the both cells were noticed. In particular, somatic cells went through rapid nuclear reprogramming and epigenetic changes through fusion to form hybrids cells with distinct genetic and phenotypic characteristics contrasted with the parent cells [189]. In synkaryons, only one nucleus was formed because of the union of the two cell types [190]. Alongside the discovery of CSCs, it has been demonstrated the way that stem cells can fuse with differentiated cells, shaping a heterokaryon, having the functions and characteristics of each of the two cell types engaged with the fusion cycle. Cell fusion was depicted as a mechanism for generating CSCs by Gauck et al. [191]. The authors revealed that the fusion between human breast epithelial cells and human breast cancer cells formed hybrid cells with explicit CSC properties, for example, the capacity with regards to colony forming spheres. Likewise, another example the spontaneous formation of heterotypic hybrids between MSCs and lung cancer cells. The newly formed hybrids cells expressed the stem cells marker prominin-1 [192] close by the expression of other stem cells like phenotypic characteristic, for example, ALDH-1, B-lymphoma Mo-MLV insertion region 1 (BMI-1), the transcription factors octamer-binding transcription factor 4 (OCT4) and sex-determining region Y-box 2A (SOX-2A) [193]. Outstandingly, these changes happen over a limited period contrasted with the genetic changes because of random mutations. Further, a few biological processes, like inflammation and hypoxia, could enhance cell fusion [194,195].

VI. Horizontal Gene Transfers between Cells

Horizontal gene transfer (HGT) or lateral gene transfer (LGT) includes a process wherein an organism transfers genetic material to another non-descendant cell [196]. Genomes of evolving cells are exposed to higher plasticity than most conserved cells, and tumour cells should reinvent themselves to proliferate in the recipient organism [197]. It was hypothesized that circulating tumour DNA was proliferated into the human body through biological fluids, and is inserted into normal stem cells, which could then be transformed into CSCs. The incorporated genes were expropriating for vertical inheritance [198,199].

VII. Genetic Instability

As stem cells age, similar to some other body cell they can gather genetic mutations; notwithstanding, the basic distinction is that all through their life span, gradual obtaining of mutations in the stem cell population and their progeny can bring about cancer [200,201]. Knowing this, stem cell biology is an essential for cancer scientists, on the grounds that tumorigenesis continues through the gathering of acquired gained substantial transformations and tumorigenesis, which may modulate gene expression. In light of their specific ability to self-renew, which requires a high rate of cell division, stem cells are the most fitting cell type to

gather chromosomal abnormalities and stochastic mutations [202-204]. As stem cells divide, acquired mutations gather in the stem cells pool over time [205,206]. Any deficiency of functional genes because of mutation during a symmetric cell division process controls the fate of stem cell – derived daughter cells, and may prompt an uncontrolled self-renewal that disturbs stem cells homeostasis and at last prompts cancer [207].

VIII. Molecular Pathways in Cancer Stem Cells

CSCs are endowed with self-renewal and high proliferative potential, characterized by both symmetric and a symmetric cell division, similar to normal stem cells [208,209]. Hence, the primary molecular mechanisms directing CSCs are the same to that of normal stem cells, which manage and coordinate embryonic development and tissue repair, especially the Wnt, Hedgehog, and Notch pathways [210].

8.1 Wnt Signaling

The Wnt pathway was recognized in the late of the 1990s as a proto-oncogene responsible for the development of cancers in transduced mice. Several pathways control Wnt signalling, with three emerging as the most significant, the "standard" Wnt pathway (likewise called Wnt/β-catenin). The Wnt/β-catenin pathway is enacted when a Wnt ligand ties to a seven-pass transmembrane Frizzled (Fez) receptor and its co-receptor, low-thickness lipoprotein receptor-related protein 6 (LRP6) or its immediate connection LRP5 [211,212]. The formation of the Wnt-Fz-LRP6 complex and the enrolment of the platform protein Dishevelled (Dvl) brings about LRP6 phosphorylation and enactment that prompts recruitment of the Axin complex to the receptors [213,214]. These occasions lead to the inhibition of Axin-interceded β-catenin phosphorylation, and consequently to the stabilization and gathering of β-catenin in the nucleus and development of complexes with TCF/LEF. These molecular events activate Wnt target gene expression, in this way establishing the mitotic spindles, directing asymmetric cell division, underpinning maintenance, and delivering differentiated cells [215]. As of late, many studies have implicated Wnt signalling in CSCs of solid tumours, i.e., glioma, and adenocarcinoma of the colon, as an essential controller of the tumour initiating cells [216-218].

8.2 The Hedgehog Signaling Pathway

The molecular mechanism of the Hedgehog (HH) pathway is started by the HH ligands binding to the Patched receptors, blocking the inhibition of Smoothened, a seven-transmembrane domain receptor, which is answerable for the activation of intracellular sign transduction by means of the glioma-related oncogene (GLI) transcription factor [219]. This protein enters the nucleus and activates the target genes of the HH. This pathway assumes a critical role during organogenesis by mediating cell-cell communication. It likewise underlies the regulation of cell proliferation and EMT.; Essential processes engaged with carcinogenesis and ensuing cancer progression [220]. Furthermore, active HH flagging may likewise be a significant cause of cancer therapy failure in cancer patients, because of impaired chemotherapeutic drug reactions or by effectively prompting more aggressive and treatment-resistant cancers [221]. HH signaling is likewise connected with CSC identification in a several solid tumours, like breast cancer, glioma, basal cell carcinoma, gastric cancer, and colon carcinoma through the regulation of stemness-related genes, i.e., OCT4, SOX2, and BMI1 [100]. Besides, HH is engaged with managing cancer spheroid formations, as seen in case of glioblastoma (GBM) neurospheres, by controlling NANOG.; nestin, BMI1, and gene expression [222].

A trial mouse model of NOD/SCID showed that the engraftment of cancer neurospheres pre-treated with cyclopamine (a medication that binds to the heptahelical bundle of Smoothened) blocked the HH signaling, hence bringing about cancer growth reduction [223]. This information showed the way that inhibition of the HH pathway can prevent clonogenic development and self-renewal of the GBM-determined CSCs (GSCs) [224]. Besides, a combined treatment of cyclopamine and 10 Gy of radiation treatment showed a significant decrease in neurosphere growth. These data featured that HH blockade could influence CSCs, which for the most part are not targeted by chemotherapy and radiotherapy alone [225,226]. Signaling pathway managing self-renewal in CSCs. Notch signaling, similar to the Wnt and Hedgehog pathways, is an exceptionally developmentally preserved pathway of cell fate determination, with significant importance across different parts of cancer biology, from angiogenesis and tumour immunity to the regulation of CSCs' self-renewal ability.

8.3 The Notch Signaling Pathway

The Notch signalling pathway was first found in a Drosophila melanogaster, and its mammalian homolog has four receptors (Notch1-4) and five Notch ligands (Delta-like 1, 3, and 4, Jagged 1, and Jagged 2), which are transmembrane proteins controlling

the correspondence between cells [227]. As a ligand binds with a Notch receptor, it releases a proteolytic cleavage of the Notch intracellular domain (NICD). This advances translocation into the nucleus to bind with the specific transcription factor CSL [228]. The NICD/CSL transcriptional activation complex is answerable for the activation of the basic helix-loop- helix (bHLH) family of transcription factors like HES.; HEY.; and HERP (HES-related repressor protein) [229]. HES and HERP are seen as primary targets/effectors of Notch, as Notch signaling depends on close collaboration among HES and HERP.; which have distinctive repression mechanisms that direct the mRNA of the target gene [230].

The dysregulation of Notch is connected with numerous malignant tumours, as Notch goes about as an oncogene and a suppressive gene, principally relying upon the environmental context and the cues involved there. For example, an upregulation of the Notch pathway is liable for GBM and malignant medulloblastoma [231,232]. Thus, various methods for silencing Notch have been explored, for example, inhibitor compounds, monoclonal antibodies, and siRNA. Co-inhibition of Notch and HH in an in vitro model of the GBM neurosphere showed a reduction in tumour growth and clonogenicity [233,234]. The CD133+ CSCs isolated from the glioma cell line were susceptible to γ-secretase inhibitors (GSI), or Notch1/2 knockdown, compared to the respective CD133-negative glioma cells [235,236]. This proof features that Notch might be viewed as a promising target for growing more successful glioma treatments [237,238]. Besides, as in ovarian cancer, CSCs are facilitated with in migration and cell invasion through Notch1 even without hypoxia, which is typically a main factor supporting metastasis [239,240]. For sure, Notch signaling is connected with CSCs of different various origins in solid and hematologic tumours, i.e., breast disease, pancreatic cancer, colon carcinoma, and acute myeloid leukaemia [241]. It has likewise been shown that the activation of Notch advances cell survival and self-renewal, and inhibits apoptosis [242]. As described in breast cancer research, unusual Notch signalling triggers CSCs to advance self-renewal and metastasis [243]. Specifically, microRNA-34a is a suppressor of Notch1 gene expression, prompting inhibition of cell proliferation activity and expansions in the apoptotic processes of breast cancer cells and stem cells [244]. An important master gene controller in breast cancer, like BRCA1, activates the Notch pathway in breast cancer cells through transcriptional up-regulation of Notch receptors and ligands [245]. Besides, BRCA1 controls JAG1 through a Delta Np63-dependant mechanism, whose role in stem cell fate is notable [246].

IX. CSCs as Novel Targets for Cancer Therapy

New Perspectives to Control Tumorigenesis Cancer treatment approaches are one of the most astonishing areas of research. Regardless of the introduction of immunotherapy, which is answerable for altogether further improved prognosis, the possibilities of recurrence and death remain extremely high. Highest quality level treatment as per oncological guidelines involves a surgery for the early stages and chemotherapy/radiotherapy for locally advanced and generally advanced cancer. CSCs appear to assume a pivotal role in cancer recurrence [247,248]. It has likewise featured the significance of focusing on this sub-population of cells, since common oncological medicines are not completely effective against CSCs, which can survive in a quiescent state and replicate after an injury, for example, those triggered by chemotherapy. Subsequently, the need to target CSCs has driven analysts to concentrate on ALDH.; presently being viewed as the best marker to distinguish and additionally target CSCs in several solid cancers. To all the more likely comprehend the role of a previously approved cell cycle gene signature associated with cancer recurrence, Masciale et al. isolated CSCs from fresh surgical lung cancer specimens by isolating ALDH high + cells [136].

It ought to be noticed that ALDH isn't just a marker yet a practical controller of CSCs. ALDH is an enzyme of the ALDH superfamily known to control cell functions related to self-renewal, differentiation, resistance to drugs and radiation. Future treatment approaches might look to find a marker ready to specifically target CSCs. Specifically, a superficial marker is expected to make it easier to foster new clinical therapies in cancer treatment. In such manner, a significant accomplishment in cellular lung cancer has recently been reached through the Cancers study of CD44+/EPCAM+ cell populations, which showed a high relationship and affinity with CSCs, recently distinguished by ALDH high cells. This could address a breakthrough for lung treatment, since it can bind and target CSCs through their surface proteins/markers. Beyond the urge to track a surface marker, and close to the way that several publications have shown the presence of stemness genes in CSCs, new systems are being done, specifically focusing on the activity of cancer stem cells, specifically on a CSC gene signature [136].

A cross-sectional review including 22 patients going through surgery for adenocarcinoma or squamous cell carcinoma of the lung investigated a huge and already known panel of 31 cell-cycle genes connected with cancer recurrence, for both early and locally advanced stages, to make more customized treatments on the future [136]. The novelty of this as of recently published cross-sectional review was in recognizing similar recurrence of genes in CSCs for early and locally advanced stages. Specifically, further analysis has uncovered that a subset of these genes is differentially expressed among stages, gathered as early

in stage I-II and locally advanced with stage IIIA.; recommending genes that were fundamental during the initial phase of the tumor and others which lead to metastasis. Besides, stemness genes, like OCT4, NANOG.; and SOX2 have higher expression in CSCs contrasted with non-CSCs [119]. A gene signature study concentrates on explored a potential RNA interference mediated down-regulation of this gene expression, including anti- apoptotic genes, to guarantee a more effective eradication of CSCs later on. For instance, in glioblastoma (GBM), inhibition of checkpoint kinase 1 (Chk1) and checkpoint kinase 2 (Chk2) activity decreased its resistance to radiotherapy [251]. L1 cell adhesion molecule (L1CAM) shRNA induced the elimination of CD133+ glioma cells, yet it didn't influence negative cells. Alongside this advanced approach, more typical however no less significant methodologies have been developed to decrease drug toxicity and chemo-resistance. Specifically, targets connected with ABC transporters have been studied as one of the main ways of lessening resistance to clinical oncological medicines. Down-regulation of ABC transporters might restrain drug efflux, making the medication continue longer inside the tumour cells, including CSCs. This would help the tumour cells' removal. Established researchers has shown that down-regulation of ABC transports ought to be normalized to prevent side effects [252]. Methodologies to quiet CSC-related genes that can diminish or inhibit their leading molecular roles, like growth and self-renewal, have been concentrated on in cervical cancer stem-like cells [253].

In tumour cells, blocking CSC signaling pathways, like AKT and signal transducer and activator of transcription-3 (STAT-3), in glioma is an effective practical approach that necessities further investigation for application in other solid tumours [254-256]. There is likewise the chance of unique CSC niches, since they address a continuous supply for these cells, preserving cancer. A new report has shown that CSCs make their niche around blood vessels, diminishing radiotherapy efficacy. Eminently, this has been described within cells from angiosarcomas (a rare vascular tumour) of the lung positive for ALDH.; which recommends a central role for ALDH in the angiogenetic process, since it has likewise been distinguished in the endothelial stem-like cells of these vascularized tumours [257]. Research gives instances of drugs that work against angiogenic factors influencing CSCs, for example, one using an in vivo mouse model to concentrate on the impact of the vascular endothelial growth factor receptor 2 (VEGFR2) antibody that, in association with a chemotherapeutic treatment, was able to decrease CSCs' subpopulation [176]. This perspective recommends that a therapeutic approach based on anti- angiogenesis can kill CSCs and addresses a promising methodology for developing new cancer treatments [176,258].

A clever way to deal with cancer treatment focused on CSCs to get through the mechanism of drug resistance in cancer. Nanoparticles (NPs) have been developed to expand the designated efficiency of drugs by expanding their stability, in this manner working with their entrance into the nucleus for a more extended lasting impact, permitting a decrease in dose and a potential reduction in adverse effects [259,260]. In any case, their immunogenicity and uneven intra-tumour dissemination frequently restrict their remedial potential and clinical application. There is a critical need to utilize cell vehicles with drug-loaded NPs. Consequently, joining nanomaterials with new nanotechnology-based drug delivery platforms, for example, exosome-based approaches, could address promising new tools [261,262]. Exosomes can be utilized as drug and miRNA delivery vectors in cancer treatment, as has been utilized in other cases [268]. Through their membrane-anchored ability, exosomes can be taken up by the cells by means of endocytosis to move their content, for example, miRNAs and therapeutic proteins [264,265].

Contrasted with liposomal and metal or polymeric nanomaterials, exosomes can overcome the requirements of poor bioavailability and diminish off-target cytotoxicity and immunogenicity. In 2016, Kim [266] found that paclitaxel-loaded exosomes got from macrophages, contrasted with paclitaxel-loaded liposomes, altogether expanded cell up-take in vitro experiments utilizing cancer lung cell lines. Li et al. [267] have adjusted the outer layer of the exosomes with a peptide-focusing on mesenchymal-epithelial transition(MET) factor gene (c-Met), overexpressed on triple-negative breast cancer cell surfaces, with the consequence of further developing the cell take-up efficiency and anti-tumour efficacy of doxorubicin. Exosomes are likewise significant in modulating CSCs by focusing on CSC-explicit signaling path ways, like the Wnt, Notch, Hippo, Hedgehog, NF-κB.; and TGF-β pathways, which are critical for the self-renewal, differentiation, and tumorigenesis of CSCs. Specific targeting of CSCs through these pathways utilizing exosome-loading inhibitors (miRNAs or siRNAs) is viewed as a promising treatment approach [268]. For instance, in lymphoma, the cells use Wnt signaling pathways to send data to adjoining cells through exosomes. Late studies have shown that exosomal Wnt from fibroblasts could prompt growth cell de-differentiation, triggering chemotherapy resistance in colorectal cancer cells and along these lines recommending that interference with exosomal Wnt signalling could improve chemo-responsiveness for additional effective treatments. Different studies involving in vivo animal models showed the significant and more potent impact of exosome-based chemotherapy than free drugs. In addition, contrasted with free drugs, the exosome-based delivery platform may fundamentally diminish side effects, while staying considerably more

effective in killing drug resistant cancer cells. Antibody response that, in relationship with a chemotherapeutic therapy, had the option to diminish CSCs' subpopulation [176]. This perspective recommends that a promising approach in light of anti-angiogenesis can kill CSCs and addresses a promising approach for developing new cancer treatments [176,258].

Target treatment intended for quiescent cells. CSCs are safeguarded inside the niche in a dormant scheme. These different synthetic nanoparticles (NPs), like liposomes, micelles, polymers, and gold nanoparticles, have been displayed to effectively convey anticancer drugs to the targeted CSCs by utilizing CSC-explicit markers, like CD44, CD90, and CD133. A study of engineered exosomes containing miRNA (especially miR-21) show they successfully downregulated target genes PDCD4 and RECK of the miR-21 in glioma cell lines [269]. In light of this information, it is feasible to develop new methodologies depending on engineered exosomes conveying tumour suppressor proteins, nucleic acid components like miRNAs, or targeted drugs working as precision medication. However, progress has been made in this field, the molecular components of exosome production and their biological roles in tumour progression need further explanation [270]. A lot more issues should be tended to before this novel methodology can turn into a clinical reality. Nonetheless, exosome-based systems in cancer treatment have shown extraordinary commitment in trial studies.

X. Conclusion

This article fundamentally discusses the new advancement of the complex roles of multipotent MSCs in tumour microenvironment, progression, and potential clinical applications. The function of CSCs in tumour microenvironment ought to be focused closer on, which is critical for development of cancer cells. The roles of miRNAs and signaling pathways in tumour microenvironment should be intensively studied, which might provide us with new means to treat cancer precisely. We ought to likewise focus on the molecular mechanism of antitumorogenic activity of MSCs, which might improve the accuracy of targeted treatment. Significantly, decreasing the growth stimulation and malignant transformation of MSCs in tumour targeted treatment will speed up clinical transformation.

XI. Abbreviations

ADSCs:	Adipose-derived stem cells
ASCs:	Adipose stromal cells
BC:	Breast cancer
CSCs:	Cancer stem cells
CXCR4:	Chemokine (C-X-C motif) Receptor type 4
CTL:	Cytotoxic T lymphocyte
CX3CL:	CX3C chemokine fractalkine
EAC:	Esophagogastric adenocarcinoma
hBM-MSCs:	Human fetal bone marrow stem cells
HCC:	Hepatocellular carcinoma
HER2:	Growth factor receptor 2
HGF:	Hepatocyte growth factor
HIFs:	Hypoxia-inducible factors
hUCMSCs:	Human umbilical cord MSCs
HSV-TK:	Herpes simplex virus thymidine kinase
hUCMSC-EVs:	hUCMSC-derived extracellular vesicles
IL-6:	Interleukin-6

IFN-β:	Interferon beta
LUAD:	Lung adenocarcinoma
LOX:	Lysyl oxidase
MSCs:	Mesenchymal stem cells
NK cells:	Natural killer cells
PDGF:	Platelet-derived growth factor
PI3K:	Phosphoinositide 3-kinase
PDGFRβ:	PDGF receptor β
PTEN:	Phosphatase and tensin homolog deleted on chromosome 10
PTX:	Paclitaxel
SDF1:	Stromal-cell derived factor-1
TGF-β:	Transforming growth factor-β
TNF-α:	Tumor necrosis factor-α
TRAIL:	TNF-related apoptosis-inducing ligand
VEGF:	Vascular endothelial growth factor.

Conflict Of Interest

All authors declare no conflicts of interest.

Authors Contribution

Authors have equally participated and shared every item of the work.

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