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Review Article

Recent Advantages of Stem Cell Therapy in the Treatment of Cancer

Arghya Bhattacharya[1]* and Arindam Chakraborty[2]

[1]Department of Pharmacology, Calcutta Institute of Pharmaceutical Technology and AHS, Uluberia, Howrah, India

[2]Department of Pharmaceutical Biotechnology, Calcutta Institute of Pharmaceutical Technology and AHS, Uluberia, Howrah, India

***Corresponding Author:** Arghya Bhattacharya, Department of Pharmacology, Calcutta Institute of Pharmaceutical Technology and AHS, Uluberia, Howrah, India.

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Abstract

Metastatic cancer cells cannot be completely erased by using the traditional surgical or chemo radiotherapy, and relapse may occur as a common things in this. On the other hand the application of stem cell based therapy gain its promise to combat with cancers and removal in a complete manner. Actually, stem cells are those type of cells that can grow at a faster rate and possess self-renewal property. Actually, it act as a novel delivery platform which target both primary and metastatic tumour foci. Besides this they are employed as a nano particle carrier not only give its therapeutic effects but also give relief from treatment side effects. Like chemotherapy may lead to destroy lots of immune cells and other good cells, where supplementation of stem cell may lead to regeneration of those immune cells inside body system. Still challenges like treatment durability and tumorigenesis require further study to improve it's therapeutic performance and acceptability. This whole review focus on the recent development in anticancer stem cell based therapy and show it's advantage, potential risks and challenging opportunities.

Keywords: Stem Cell; Cancer; Stem Cell Therapy; Challenges; Application

Introduction

Cancer is a type of disease which is caused by the uncontrolled division of abnormal cells in specific parts of the body. Still now in both developing and developed country it may lead to death. From the very beginning still now though chemotherapy, surgical resection and fractioned radiotherapy are treated as the only way to combat this disease still they all carry a lot of adverse effects, off targets and sometime drug resistance may also occured. Moreover, metastatic cancer cannot be treated completely with this therapy as well.

In this situation stem cells which are special human cells possess some unique property like migrating itself towards the cancer cell, secreting several bioactive factors and immuno suppression which ultimately boost tumour targeting and evades obstacle which impede current gene therapy strategies. Recently pre clinical stem cell oriented treatment gain promise to be used in targeted anti-cancer therapy. This review summarize the recent development in anticancer stem cell based therapy and show it's advantage, potential risks and challenging opportunities

Stem cell definition and it's source

Stem cells actually are those cells which can renew itself indefinitely and can be differentiated in to different cell types [1]. Thus, it plays a vital role in tissue re-generation and in homeostasis [2]. Several types of Stem cells available, among which the two main types are a) Embryonic stem cell (ESCs) and b) somatic stem cell (SSCs) or which also can be called as adult stem cell. This adult stem cell can be differentiated into any cell type like Neural Stem cell (NSCs), Mesenchymal stem cell (MSCs), Hematopoietic stem cell (HSCs), Endothelial progenitor cell (EPCs) [3].

ESCs and iPSCs

ECs has the capability to differentiate itself in various types of cells except placenta and thus they are used in all pluripotent cell culture (*in vitro*) evaluation as a key marker [4]. Instead of this property, for some ethical issues it is restricted and as in replace induced pluripotent stem cells, derived from adult somatic cells are used [5].

NSCs

NSCs has its own self renewal property and can differentiate itself into astrocytes, neurons etc. Expression of several markers like SOX2, NESLIN is found in NSCs [6]. Due to this property it can be used to treat brain, prostate [8], breast [7] and lung cancer [9].

MSCs

Basically it is derived from bone marrow and it can be isolated and grown in INVITRO media. It has it's property to differentiated into mesodermal cells of cartilage, bone, muscle and connective tissue.

HSCs

Among all cells of blood lineage HSCs are primordial and found in bone marrow. It mainly helps to generate mature blood cells by proliferating and differentiating lineage restricted progenitor.

EPCs

It plays a key role in vascular regeneration [10]. It plays its role in cancer therapy by transfecting or coupling with anti-tumour drug or angiogenesis inhibitor [11].

CSCs

It is almost like stem like cancer cell and can be obtained from patient tissues and cell lines of different cancer type. It has it's own self renewal property and can be differentiated into other nonstem cancer cell and repel traditional therapy [3].

Stem cell properties

Basically main property of stem cell is to differentiate and self renewal. Besides of these, they also have immuno suppressive, anti tumor and migratory properties. As they possess growth factors and cytokines, they regulate the host's innate and cellular immune pathways [12,13]. Along with these, they are also capable of secreting the secrete factors like CCL2/MCP1 and also play a major role by interacting and co-culturing the phenotype of tumor cells and produce intrinsic antitumor effect [14]. Human stem cells which are originated from chemokine cancer cell interaction possess intrinsic tumor tropic properties. They also have their migratory properties, which first studied in Xenograft mouse model [15]. NSC migration to tumor is accelerated by hypoxia condition, which ultimately activates the expression of chemoattractants. Directional HSC model, which actually rely on the interaction between chemokine, CXCL12 and CXCR4 [16]. The Stromal Cell Derived Factor 1(SDF1)/CXCR4 plays a vital role of migration of stem cells [17-21]. For better effectiveness stem cells sometime modified with higher levels of chemokine receptor to release more chemokine [22]. It is proved in *in vitro* and Xenograft mouse model that over expression of MSCs by CXCR4 migrates towards the glioma cells and more effectively work than control MSCs. Controlled release of chemokines from different biomaterials may increase the recruitment of stem cells. It is also reported that site specific homing of MSCs towards cellular polycaprolactone, constantly may release SDF-1 with micro delivery device *in vivo*. By these two main strategies the homing efficiency improved and also the treatment outcomes.

Challenges to stem cell therapy

Treatment durability

In spite of strong initial therapeutic effect, tumors may relapse. Only by using a single agent based stem cell therapy may not eliminate tumors. That's why an optimum drug combination is wisely chosen and required [6]. Several combinations are tested to make the treatment more efficient and long durability. Like combination therapy of IFN-β immunotherapy and chemotherapy by using a prod rug gene system has showed synergistic therapeutic effects against human colorectal cancer [23]. By irradiating the tumor cells, it helps to induce the production of factors which ultimately stimulate MSC invasion through integral basement membranes, which in a result helps to increase the numbers of MSCs in tumors [24]. The combination of oncolytic virotherapy and chemo radiotherapy helps to minimize disease volumes and make glioma cells sensitize to CRAD-S-pk7during radio therapy. Epidermal Growth Factor Receptor (EGFR), mutated, in over expressed condition in tumors it produce poor prognosis and the survival is shortened [25]. Stem cell delivered immunoconjugates of EGFR specific nanobodies and TRAIL combination may enhance treatment outcome [26].

Potential tumorigenesis concerns

Normal stem cells possess some features including self renewal, differentiation and epithelial to mesenchymal transition capacities. There is evidence of increase in cancer risk, like tumor formation

after four years of fetal neural stem cell transplantation for ataxia-telangiectasia [27]. MSC secretion of chemokine CCL5 which is promoted by breast cancer cells, acted in paracrine type, which ultimately increase cancer cell motility, invasion and metastasis. The metastatic capability of increased breast cancer cell was reversible which rely on CCL5 signaling through CCR5 chemokine receptor. That's why in the tumor micro environment, MSC facilitates metastasis by reversibly changing cancer cell phenotypes. *In vitro* cell culture condition produce stress induced genomic instability and promote the malignant phenotype. So, optimization is required for MSC expansion for clinical use. By all these evidence it is reported that the fate of stem cells ultimately rely on culture environment and the implanted stem cells play a key role in growth of certain tumors. Rather than ESCs and iPSCs, multipotent NSCs, MSCs and HSCs seemed to be safe for clinical use purpose [28]. But generally maximum studies rely on pluripotent stem cells that is highly tumorigenic. There are several way of eliminating neoplastic transformation possibilities. First of all the undifferentiated stem cells which are maximum tumorigenic should be excluded from clinical preparation by applying antibodies that ultimately target specific surface displayed biomarkers. The differentiation of stem cells ultimately down regulates the display of those biomarkers. Monoclonal antibodies can promote the fluorescence activated all sorting or magnetic activated cell sorting of undifferentiated, pluripotent stem cells which modified with fluorochromes or super magnetic chelates. The second way in which the iPSCs differentiated, which includes monitoring the expression of differentiation of lineage specific genes. The differentiated cells which are identified can be sorted using recombinant reporter proteins. The GFP and other proteins of similar types play a key role as reporters of undifferentiated VS. differentiated cells. By transformation of undifferentiated pluripotent stem cells, they can express GFP which ultimately emit telltale fluorescence upon illumination with specific wavelength as long as they remain undifferentiated. This promotes the sorting through laser ablation. Thirdly undifferentiated cells can be destroyed by utilizing toxic antibodies or antibody guided toxin [29]. Fourthly undifferentiated stem cells may be destroyed by utilization of cytotoxic agents, which are used specifically to eliminate pluripotent stem cell reduced tumor. Enzyme Stearoyl-coA desaturase1,which is involved in the metabolism of mono unsaturated fatty acid and induce apoptosis in treated cell is inhibited by PluriSIn#1.This PluriSIn#1 also specifically destroy undifferentiated iPSCs and ESCs [30].The fifth way is to sensitize the tumorigenic stem cells towards pro drugs through transformation using suicide genes. Finally, differentiated refractive stem cells can be destroyed by self inducing transgenic expression of recombinant human DNases. To improve the safety, toxic reagents independent feedback loop is produced and target for differentiated stem cell. iPSCs Which differentiated into endothelial or myocardial lineages were transfected with human recombinant DNASE1, DNASE1L3, DNASE2 and DFFB, which are guided by antiSSEA-4 and anti-TRA-1-60 synthetic antibodies [31]. Thus iPSCs maintain its pluripotency and specific cell surface display profile. Thus, these six Strategies may help to safe guard against tumor transformation.

Application of stem cell therapy in the treatment of cancer

HSC transplantation

In the treatment of lymphoma, myeloma or leukaemia, HSC transplantation is one of the potential approach now a days [32]. There are several clinical trials are going on to use HSC Transplantation in different types of cancer like Brest cancer, brain cancer, sarcomas, neuroblastomas in the combination with chemotherapy or different immunotherapy but there are different major drawbacks like when allogenic HSC treated with any immunosuppressive drug it shows less effectiveness as well as some side effects also [33].

MSC transplantation after cancer treatment

For serious cancers there are several treatments involving high-dose therapy, invasive tumour removal, which can damage the normal tissues and hematopoietic system as well. Introduction of MSCs can help to maintain the undifferentiated state and proliferation of HSCs which resulting in high treatment outcome treatment outcome [34]. For the patients with refractory GVHD, MSCs having immunomodulatory effects can be effective to reduce the strong immune responses. There is a promising outcome with no potential side effects have been seen in case of co-transplantation of MSc and HSCs [35]. MSCs are very useful for the speedy recovery of injured organs and it can be helpful to increase the body tolerance to high dose chemotherapy for the improvement of tumour killing effects. In adults with steroid resistant GVHD, a multi-centre trial (NCT02923375) is going on to test the tolerability, efficacy and safety of the mesenchymoangioblast-derived MSC [36].

Stem cell a potential therapeutic carrier

Stem cell carrier can be used in cancer treatment due to (1) Lower systemic adverse effects (2) The protection of therapeutic agents from biological degradation (3) Higher levels therapeutics of stems cells because of their intrinsic tumour targeting activities.

Genetically modified stem cells

To increase the expression and secretion of soluble factor like prod drug converting enzyme or tumour toxic cytokines/ chemokines, the approach of genetically modified stem cells (MSC, NSC) can be used. This system formerly known as "Suicide Gene therapy" or "Gene directed enzyme prod rug therapy". As example, 5-fluorocytosine (5-FC) can be converted effectively into tumour-toxic 5-fluororacil (5-FU). In same manner a less potent prod drug 'irinotecan' can be metabolize into SN-38 in the present of carboxyl esterase, which is the 1000 fold more toxic compound. There are several test of phase-I, phase-II clinical trials on the Gene directed enzyme prodrug therapy has been reported [37-39].

Stem cell Therapy	Drug(s)	Tumour Type
CD-expressing NSCs	5-FC	Recurrent high-grade gliomas.
HSV-TK-expressing MSCs	Ganciclovir	Advanced, recurrent or metastatic gastrointestinal adenocarcinoma.
CD-expressing NSCs	5-FC and Leukovorin	Recurrent high-grade gliomas.
INF-β-expressing MSCs	-	Ovarian cancer.
TRAIL-expressing MSCs	-	Adenocarcinoma of lung.
ICOVIR5-infected MSCs	-	Metastatic and refractory solid tumours.
OMV-infected MSCs	-	Recurrent ovarian cancer.
Ad5-DNX-2401-infected MSCs	-	Recurrent high-grade gliomas.

Table 1: Stem cell therapy in different types of tumour.

Nanoparticle based carriers of stem cell therapy

Nanoparticles carrier are mainly used because of the presence of insoluble chemotherapeutic reagents in higher concentration and it can also protect them from degradation in any unwanted biological conditions. [40,41]. Stem cell as a NPs can overcome some limitations of using single nanoparticle as delivery agents, such as inefficient solid tumour dissemination, failed to target Micro metastatic lesions etc. Using stem cell can reduce the unwanted uptake of nanoparticle by mononuclear cells and can also protects the therapeutic agents from host immunosurveillance [42-45].

Virus therapy

Oncolytic viruses can replicate in tumour cells. Oncolytic viruses can increasingly spread in the in the body and it can hide from immune system as well. Oncolytic virus transduced NSCs show better antitumor effect than the virus than the virus alone in GBMs [46]. Virus delivery system by MSCs is also a very promising treatment for cancer. In a report it has been shown that MSCs mediated delivery of oncolytic herpes simplex virus (oHSV) in GBM resection mouse model enhanced the anti-tumour effect of the virus. In this approach MSCs dynamically infected GBM cell can produce the oHSV which in case is used to kill the tumour cells *in vitro* and *in vivo* [47,48] oHSV and TRAIL in combination can effectively avoid tumour resistance. Tumour cell apoptosis can be effectively induced by oHSV/TRAIL loaded MSCs [49].

Production of immune cells from stem cell

In anti cancer immunotherapy natural killer cell and shimmery antigen receptor t cells can be used successfully. This clinical grade immune cells can be collected from the own patients and then they are further are further activated, genetically transduced with CAR constructs, expanded and then again they are reinfused to the patient [50]. It is very challenging for the patients who have gone through heavy chemotherapy or with higher ages, to control the quantity and quality of the cells. These CAR immune cell's activities have some limitations likely their short lived effectors lived effector cells, so it is necessary to generate CAR from some other sources which can be used to expand this immunotherapy to a large number of patients number of patients [51]. In NK cell or T cell initiating cytokines containing growth medium, incubation of the stem cells comes under the differentiation process. As example, to introduce T cell differentiation hESCs and bone marrow stromal cells(OP9) were cultured in the SCF, IL-7 and FLT3L containing medium and to introduce NK cell differentiation, stem cell factor (SCF), IL-3, IL-7, IL-15 and fms-like tyrosine kinase receptor-3 ligand containing cytokines are used [52].

Stem cell vaccine

CSCs have a very important role in tumour formation and progression, so it is very effective to choose therapies which can target the CSCs in cancer treatment. Due to the high immunogenicity the anticancer vaccines are very promising amongst various CSE targeting approaches [53]. These anti cancer vaccines can be harvested from different on cofetal peptides or CSC/ESC/iPSC based whole cell. Vaccines produced by ESC/iPSC can be more effective to treat cancer. They are mainly working on teratoma formation and autoimmunity introduction [54]. This vaccine based treatment should be used as profile lactic treatment rather than and as therapeutic treatment. Tumours having strong immunosuppressive micro environment can reduce the effectiveness of the vaccine treatment but if it is used with other combination therapies such as surgery, chemotherapy, radiation therapy etc, it would be more beneficial and it will enhance the anti-tumour immunity of the vaccine treatment [55,56].

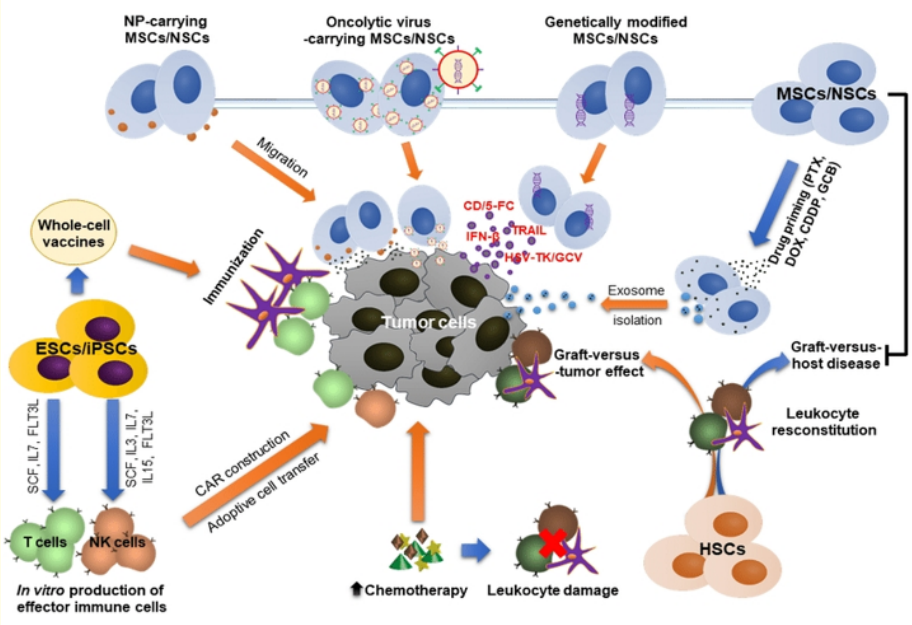

Figure 1: Strategies for the application of stem cell therapy in the treatment of cancer. (1) HSC transplantation has been used for the reconstitution of blood-forming cells and leukocytes after heavy chemotherapy or radiotherapy. (2) ESCs and iPSCs can be used for the production of effector immune cells that are then CAR constructed for adoptive cell transfer technology. In addition, ESCs and iPSCs can be potential sources for the production of anticancer vaccines. (3) MSCs/NSCs are effective to deliver genes, NPs and OVs to tumour niche due to their intrinsic tumour tropism. In addition, exosomes extracted from the culture of drug-priming MSCs/NSCs can be used to target the drugs to tumour sites. Moreover MSCs are capable of reducing GVHD in HSC transplantation.

Conclusion

Stem cell based technology may provide several opportunities for cancer therapy. Stem cell itself reach toward the solid tumour and micro metastatic lesions and produce site specific anti-tumour agent delivery. Stem cells can be structured to express several anti-tumour agents which overcome the short half lives of conventional chemotherapeutic agents. A proper knowledge of fundamental stem cells mechanism may improve stem cell based regenerative medicine and also anticancer strategies which will ultimately play crucial role for wide spread clinical utilization of stem cell based therapy.

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