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STEM CELLS: A BOON TO CANCER THERAPY

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ABSTRACT

Metastatic cancer cells usually can't be eradicated using traditional surgical or chemo radio therapeutic ways & disease recurrence is extremely common following treatment. On other hand stem cell based therapeutic methods have emerged as terribly engaging treatment choices over the past decades. In present days, stem cells are used as courier vehicles particularly in cancer therapy to deliver variety of targeted proteins & viruses. Multiple types of stem cells have reported to show inherent reaction towards tumors. They have additionally been used as virus & nanoparticle carriers to enhance primary therapeutic efficacies & relative treatment side effects. As well, these cells can be used in immunotherapy, regenerative medicine, cancer stem cell targeted therapy, & anti-cancerous drug screening applications. However, while using the stem cells for treatment of human cancers seems technically possible, challenges like treatment enduringness & tumorigenesis necessitate further study to enhance therapeutic performance & applicability. This review gives a detail on recent progress towards stem cell based cancer treatments & summarizes treatment advantages, opportunities, challenges & facilitated translation from experimental to clinical studies.

KEYWORDS: stem cell, targeted cancer therapy, cell carrier, delivery agent.

INTRODUCTION

Cancer is a major source of death in both developed & developing countries due to increasing population and aging. Over the last 60 years, many diseases that cause deaths have dramatically decreased but a cancer death has not been reduced. However, cancer is clearly known as a heterogeneous disease & the awareness is rising that intra-tumoral heterogeneity helps in therapy failure & disease progression. Cancer is given medical care or attention

using surgical resection, fractionated radiotherapy & chemotherapy but treatment related side effects, off- target effects & drug resistance resist the capability of various therapeutic options. Also metastatic cells normally can't be eliminated by conventional therapies and there are many cases of their recurrence. Therefore, researchers are running to develop new, innovative, effective, beneficial therapies with low or no toxicity in normal cells.

Stem cells have special properties like migration towards cancer causing cells, secretion of bioactive factors & immuno-suppression which encourage tumor targeting. Preclinical stem cell based plans therefore used in targeted anti- cancer therapy applications. Basically, adult stem cells are now the base of all successful atom cell based therapies. In a living organism, The first role of an adult stem cells are to maintain & repair the tissue withinin which adult stem cells are found however current thinking suggest that these stem cells have more importance as immuno-modulators with their regenerative characteristics exists due to trophic paracrine impacts instead of true regeneration. In general, all the cancer treatments including surgery, hormonal therapy, anti- angiogenesis therapy & immunotherapy are lack of efficacy in terms of long- term outcome because of their failure to target cancer stem cells& toxicity due to non specific effects on normal cells. This review gives a brief information about recent anti- cancer stem cell therapy studies & recognize advantages, opportunities & prospective challenges.

Stem Cell Definition and Sources

Stem cells are known as biological cells that have ability to: 1) self renew i.e. ability to produce same type of stem cells. 2) can distinguished into different type of cells. 3) form single cell derived clonal cell populations.[1] 4) cells have potential of tissue regeneration and repair.[2]

Stem cells can be clearly divided as 'Embryonic' (ESCs) or 'Somatic' (SSCs). SSCs differ into cell type including hematopoietic stem cells (HSCs), neural stem cells (NSCs), endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs) and others.[1][3]

ESCs are pluripotent, can differ into all cell types except in placenta.[4] Therefore used as gold standards in screening of all pluripotent cells cultured in vitro.[5] They can be differ into all derivatives of germ layers: endoderm, ectoderm & mesoderm.

NSCs can self renew & differentiate into astrocytes, neurons and used to treat brain, breast[6], prostate[7] & lung[8] tumors. MSCs obtained from bone marrow and differed into mesodermal cell which includes adipose tissue, bone, cartilage, connective tissue, stroma, muscle & tendon. HSCs primitive of blood lineage cells, found to be in bone marrow & produce mature blood cells through proliferation & differentiation of lineage restricted progenitors. EPCs are main drivers of vascular regeneration.[9] EPCs are used in cancer therapy, coupling with angiogenesis inhibitors or antitumor drugs.[10]

Stem Cell Properties

Other than self renewal and differentiation like properties stem cells have immunosuppressive, antitumor & migratory properties. Stem cells demonstrate cytokine & growth factors which regulate host innate & cellular immune pathway. [11][12] Stem cells also secrete factors like CCL2/MCP-1 & interact with tumor cells, changing tumor cell phenotypes & exerting intrinsic antitumor effects.[13] Stem cells are able to treat excrescence in kids with inherited or inborn mistakes of metabolism by replacing the faulted cells in bone marrow with new & non defected cells.[14] Stem cell is "uncommitted" till it receives a sign to bew converted into a specialised cell.

Stem Cell Modifications for Cancer Therapy

Most frequently NSCs & MSCs are modified for using in cancer therapies. General modifications include enzyme/prodrug therapy, secreted agents, viral therapy & nanoparticle carriers.

Enzyme/prodrug therapy

NSCs & MSCs exhibit enzymes that are able to change non-toxic prodrugs into cytotoxic products ultimately damaging the tumor cells when modified stem cells are transplanted into tumor- bearing models. Enzyme/prodrug therapy also called as "suicide gene therapy" was the first therapy which entered into clinical trials.[15] The enzyme which is currently used in enzyme/prodrug therapy is Cytosine Deaminase (CD). CD changes the prodrug 5-fluorocytosine (5-FC) into the toxic compound 5- fluorouracil. Combination of CD with NSCs & MSCs inhibited glioblastoma (GBM) cell growth[16] & also suppress tumor growth.[17] Herpes simplex virus- thymidine kinase (HSV-TK) has also been used in suicide gene therapy.[18] HSV-TK converts the prodrug monophosphorylate ganciclovir (GCV) to cytotoxic triphosphate ganciclovir (GCV-TP). GCV-TP merges into nearby cells DNA throught the division resulting in cell death via DNA polymerase inhibition.[19]

Secreted agents

Stem cells function as *in situ*, secreting antitumor agents for longer period of time & suppressing different cancer therapy limitations like high systemic toxicity & short drug half life. One of the mostly used secreted therapeutic agents is TNF-α- related apoptosis- inducing ligand (TRAIL) which induces tumor cell apoptosis.[20] But its short half life reduces its therapeutic effectiveness *in vivo*.[21] This can be improved by encapsulating TRAIL-expressing stem cells in a synthetic extracellular matrix which is introduced into the GBM resection cavity after surgical debulking[22] and the encapsulated cells release the therapeutic molecules continually. By this way malignant & invasive brain tumor re growth delays & survival in mice increases. Stem cells can be changed for selective delivery of growth inhibitory proteins like IFN-β rendering the micro environment inhospitable to tumor growth.[23]

Viral therapy

Oncolytic Viruses (OVs) replicate in tumor cells. They have spreads into the body & hide from immune system. OV- transduced NSCs have ability to home to tumor cells & show better antitumor effects than viruses alone against GBMs *in vivo*.[24] Virus delivery by MSCs is additionally a promising approach for targeted cancer treatment. When oncolytic activity of attenuated measles virus added with immunoprivileged & tumor tropic properties of MSCs, they could counter hepatocellular carcinoma.[25] Oncolytic herpes simplex virus when combined with TRAIL effectively avoids resistance in tumors & induces tumor cell apoptosis.[26]

Nanoparticle carriers

Nanoparticle carriers (NPs) contain high concentration of insoluble chemotherapeutic reagents, which protect them from degradation in harsh biological environment. Limitations such as failure to target micro metastatic lesions, inefficient dissemination in solid tumors can be take off by using stem cells as NP delivery agents.[27][28] Also NP can protect therapeutic agents from host immunosurvillance.[27] Also NP could act as delivery vehicles in brain tumors.[29] Thus, stem cell mediated NP- based drug delivery shows great promise in cancer treatments.

OTHER APLLICATIONS OF STEM CELL IN CANCER THERAPY

Regenerative medicine

Besides having self renewal & differentiation capabilities; after chemotherapy, stem cells can also be taken in use to repair human tissue. Transplanting HSCs has been clinically used to simplify the lifelong hematological recovery after the treatment of malignancies with high dose radiotherapy or chemotherapy. This treatment aims to improve bone marrow under marrow failure conditions & also to treat blood cell genetic diseases. Transplantation & successful engraftment of only one HSC can reconstitute hematopoiesis in recipients.[30][31] iPSC therapy is useful in replacing & repairing iPSCs of cancer patient which is damaged by chemotherapy, radio therapy or surgical treatment. Currently only a few types of human-iPSCs derived cells (e.g. hepatyocytes) have been successfully introduced in animal models.[32][33]

Immunotherapy

Allogenic HSC transplantation with an immune – mediated antitumor effect should be proper to cure some hematological malignancies.[34-36] Tumor associated antigens like genes encoding chimeric antigen receptors (CARs) or T- cell receptors (TRCs) make HSCs attractive for use in cancer immunotherapy.[37][38] Other immunotherapy approaches which could be beneficially potential are patient specific iPSCs.[39][40]

Targeting CSCs

CSCs are multipotent, having property of self renewing & also have high proliferative capacities, making a donation to rapid activation of tumor invasion & metastasis. Therefore, targeting CSCs is vital to ensuring high therapeutic efficacies & preventing tumor recurrence because CSCs have ability to attract normal stem cells, so normal SCs can be used to target CSCs in cancer therapy. Interactions between normal stem cells & CSCs suppress tumor proliferation, angiogenesis, metastasis & reduce inflammation & apoptosis.[41,42]

Anticancer drug screening

In addition to treating cancer directly, iPSCs can be used to screen new anticancer drugs. Differing patient cancer tissue derived iPSCs generates cell types which will be more biologically associated with human tumors than presently available drug screening techniques, like traditional cancer cell lines, mouse xenografts models & mouse tumors. Conjointly hepatotoxicity prevents several potential antitumor drug from being clinically

applied, & can be screened for using hepatyocytes produced from human iPSCs with various genetic backgrounds.[43]

FACTORS THAT INFLUENCING STEM CELL THERAPIES

Stem cell type

In anti cancer therapy, the choice of stem cell type depends on cell- specific characteristics & therapeutic requirements. Autologous HSC transplantation is frequently used to treat hematologic & non hematologic malignancies such as to rescue hematopoiesis after high dose chemotherapy.[44] For assessing candidate antitumor drug toxicities, iPSCs are better than other SCs.[45]

While stem cells show similar properties, their effectiveness may differ. Ahmed, et al. compared NSCs & MSCs as carriers for an oncolytic adenovirus in a glioma model & concluded that both stem cells types hold up intracellular adenoviral replication, but a log more virus was released from NSCs than from MSCs ($p < 0.001$). NSCs show superior therapeutic efficacy in intracranial tumors compared to MSCs.[46]

Route of transplantation

The route of stem cells delivery plays an important role in anti tumor therapy. [49] It must consider target pathology, therapeutic objectives & patiently risk- benefit profile. In murine models of GBM, efficient NSC delivery is achieved by contra lateral injection into the tumor site. [47] NSCs delivered intranasally can also efficiently migrate to tumor tissues. This approach can be used to avoid intravascular delivery related complications such as pulmonary embolism, obstruction by the blood brain barrier & infractions.[48]

Currently poor survival of NSC grafts can be prevented by transplantation of stem cells using biocompatible devices. Hansen, et al. reported three dimensional extracellular matrices based substrate (3DECM), which is purified from engineered skin cultures, and provide an efficient clinical administration route for cell grafts. 3DCEM retain the uncommitted differentiation of embedded NSCs *in vitro*.[49]

Cell number & transplantation

Treatment results are disturbed or affected by transplantation cell numbers & transplantation timing. Patients with oncohematological disease may results in inefficient hematopoietic component replacement if there is an insufficient number of transplantation of HSCs & also

there may be relapse of disease easily.[44] There may be an increase in the risk of tetratauma formation or ectopic engraftment if there is too large number of transplanted cells. Thus no. of cells for dominant treatment should be optimized.

Stem cell efficacy therapy depends on administration timing like NSCs should be given before ionizing radiation (XRT) & temozolomide (TMZ). It is reported that loaded NSCs given to GBM43 xenografted animals prior to XRT- TMZ treatment increased the median survival by 9 days, over that of animals receiving a reverse schedule. [50] The result of this test was that 33% of mice receiving NSCs prior to TMZ- XRT lived ≥ 70 days, compared to only 9% of mice receiving reverse regimen. Also, loaded NSCs administration before TMZ-XRT treatment promoted mouse brain tumor cell apoptosis.

For oncolytic virotherapy, carrier cells must first accumulate in tumor beds & then viral progeny released to allow targeted delivery of functioning virus.[51] Thus oncolytic viruses delivered via NSCs should have replication cycles appropriate for NSC tumor - homing abilities.[52]

CHALLENGES TO STEM CELL THERAPY

Treatment durability

Tumors commonly relapse regardless of strong initial therapeutic effects. As in most chemotherapy, using a single agent with stem cell therapy generally cannot eliminate tumors. Therefore, combination of drugs should be selected. [53]

Many combination therapies have been tested to improve treatment durability. For example, IFN-β immunotherapy combined with chemotherapy by using a prodrugs/suicide gene system shows synergistic therapeutic effects opposite the human colorectal cancer.[54] Also combining stem cells based oncolytic virotherapy can minimize residual disease volumes & sensitize glioma cells during radiotherapy.[50] Epidermal growth factor receptor (EGRF), which is mutated & over expressed in various tumors & is associated with poor prognosis & shortened survival.[55] TRAIL combined with stem cell- delivered immunoconjugates of EGFR- specific nanobodies enhanced treatment outcomes.[56]

Potential tumorigenesis concerns

Normal stem cells possess some common characteristics with CSCs, including self renewal, differentiation & epithelial-to-mesenchymal transition capacities. But stem cells also have a

risk of increasing.[57] Thus transplanted stem cells highly require additional study for prevention of tumor formation.[50] Increased breast cancer cell metastatic capability was reversible & dependent on CCL5 signaling through the chemokine receptor, CCR5. Therefore, MSCs in the tumor facilitated metastasis by reversibly changing cancer cell phenotypes.[58] Also *in vitro* cell culture conditions may cause stress induced genomic instability, promoting the malignant phenotype. Mutation can also be related due to oxygen tension[59] & matrix elasticity.[60] Therefore, optimization of in vitro culture conditions is important for MSC expansion for clinical use. Thus stem cell fates largely dependent on culture environment & implanted stem cells contribute to the growth of certain tumors or produce tumors themselves.[61]

Multipotent NSCs, MSCs & HSCs are much safer for clinical use than ESCs & iPSCs. Recent studies focuses that how pluripotent stem cells are highly tumorigenic. There are 6 techniques to eliminate any kind of possibility of neoplastic transformation.[62]

1st, undifferentiated pluripotent stem cells(tumorigenic), can be excluded from clinical preparations by using antibodies which target specified surface displayed biomarkers. Monoclonal antibodies facilitate fluorescence activated cell sorting or magnetic activated cell sorting of undifferentiated pluripotent stem cells. 2nd, directed differentiation of iPSCs involves the monitoring the expression of differentiation lineage specific genes. Differentiated cells can be identified & sorted using recombinant reporter proteins. 3rd, undifferentiated cells can be killed using toxic antibodies or antibody- guided toxins. As for Ex. monoclonal antibodies against claudin-6 will guide toxins to those stem cells for selective, targeted killing.[63] 4th, undifferentiated stem cells may be eradicated using cytotoxic agents, which might be applied to kill pluripotent stem cells that might turn into tumors. PluriSIn#1 inhibits stearoyl- CoA desaturase-1 an enzyme involved in monosaturated fatty acid metabolism & induces apoptosis in treated cells.[64] PluriSIn#1 treatment selectively eliminates undifferentiated iPSCs & ESCs.[65] 5th, potentially tumorigenic stem cells can be produced to form prodrugs through the transformation process by using suicide genes.[66] Finally, differentiated refractive stem cells will be removed through self-induced transgenic expression of recombinant human DNases. To this end, & to improve treatment safeties & efficacies, a toxic reagent independent feedback loop was developed to select for differentiated stem cells.[67] These six strategies could safeguard against tumor transformation in stem cell population.

CONCLUSION

In present days, cancer treatment entered into an new exciting period, with traditional therapies such as radiotherapy, chemotherapy & surgeries on one side while the stem cells on the opposite hand. Aside from their well known role in immune- reconstitution, the stem cells have attracted a lot of attention mainly with the new gene technologies allowing more focused delivery of the anti cancer agents. Stem cells migrate to solid tumors & micro metastatic lesions, facilitating site specific anti tumor agent delivery. Stem cells are often engineered to stably express a range of antitumor agents, controlling the short half-lives of conventional chemotherapeutical drugs. The recent progress in both stem cells & anticancer gene studies has nice potential for exploitation in new efficient cancer therapies. There is a clinical demand for a lot of remedies to exchange present symptomatic anticancer therapies. A better understanding of fundamental stem cell mechanisms will improve stem cell based regenerative medicine & anti cancer strategies, & is imperative for more widespread clinical utilization of stem cell based therapies.

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