Review Article

Cancer stem cells targeted therapy: A changing concept in head and neck squamous cell carcinoma

Adesh S. Manchanda[1], Harmandeep K. Rai[2], Manvir Kaur[2], Paras Arora[2]

[1]Department of Oral and Maxillofacial Pathology, [2]Department of Dentistry, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar, Punjab, India

Abstract

Identification of cancer stem cells (CSCs), their multilineage potential, and their ability of self-renewal have revolutionised the current concepts of cancer treatment. The suspected role of CSCs in cancer initiation, progression and relapse with the observed resistance to conventional cancer treatments has led to the development of more specific and targeted therapies. Identification of the properties of stem cells (SCs) and their potential for localisation in cancer has made targeted anti-cancer treatment possible by incorporating some modifications into these SCs. The same concept has been applied to the treatment strategy for head and neck squamous cell carcinoma (HNSCC) to control the relapse and improve the mortality rates in patients. This review aims to discuss the role of CSCs in the course and relapse of HNSCC, various surface markers for their identification and SC-targeted therapy options for the treatment of HNSCC, with a highlight on the advantages, shortcomings, opportunities and challenges to SC therapy in head and neck squamous cell carcinoma, treatment and scope for future research.

Keywords: Cancer stem cells, cancer therapy, stem cell therapy

Address for correspondence: Dr. Adesh S. Manchanda, Department of Oral and Maxillofacial Pathology, Sri Guru Ram Das Institute of Dental Sciences and Research, Mall Mandi, Amritsar - 143 001, Punjab, India.
E-mail: adesh_manchanda@yahoo.com

Submitted: 29-Aug-2024, **Revised:** 05-Sep-2024, **Accepted:** 09-Sep-2024, **Published:** 15-Oct-2024

INTRODUCTION

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, according to the International Journal of Cancer Report.[1] Head and neck squamous cell carcinoma (HNSCC) is the 8th and 13th most common malignancy in the world for males and females, respectively, with a predominance of oral squamous cell carcinoma (OSCC).[2] India has the highest incidence of OSCC due to habits such as tobacco chewing, smoking, betel quid, and areca nut, which are important risk factors. Despite the improvements in the diagnosis and management of HNSCC, long-term survival rates have improved only marginally over the past decade. Research has shown that HNSCC and the devastating diseases associated with a high rate of recurrence after treatment with conventional clinical therapies, including surgery, ionizing radiation, hormonal therapy and systemic chemotherapy, generally lead to the death of patients. Therefore, the establishment of molecular events underlying cancer initiation and progression into locally invasive and metastatic diseases is of major interest in basic cancer research as well as for the development of new effective clinical therapeutic options against recurrent and lethal cancers.[3] Recent advances have led to the identification of specific oncogenic products

Access this article online

Quick Response Code:

Website: https://journals.lww.com/JPAT/

DOI: 10.4103/jomfp.jomfp_248_24

How to cite this article: Manchanda AS, Rai HK, Kaur M, Arora P. Cancer stem cells targeted therapy: A changing concept in head and neck squamous cell carcinoma. J Oral Maxillofac Pathol 2024;28:455-63.

that are implicated in the malignant transformation of adult stem/progenitor cells into leukemic or tumourigenic and migrating cancer stem/progenitor cells during cancer progression, which exhibit self-renewing capacities and are responsible for tumour maintenance and metastasis.

Two main hypothetical models have been put forward to explain neoplasm's origin, progression and reoccurrence. The stochastic model states that a tumour is made up of homogenous cells, each having the capacity to initiate, propagate and spread the neoplasm; however, only some of these cells have the benefit of tumour evolution due to numerous discrete mutation accumulations and microenvironmental signals. The other model of cancer stem cells (CSCs) states that CSCs are self-sustaining and have an extraordinary ability to divide and result in a variable descent of cancer cells. Researchers showed that both models explain certain aspects of HNSCC. The stochastic model explains a wide range of pre-neoplastic areas away from the surgical margins, responsible for secondaries and recurrences, whereas the CSC model explains heterogeneity in HNSCC and distant metastasis.[2] CSCs constitute a small minority of neoplastic cells within a tumour and are defined operationally by their ability to seed new tumours. For this reason, they have also been termed 'tumour-initiating cells.' Identifying and understanding these CSCs is vital to devise a targeted and specific therapy against these cancer cells with minimal trauma to surrounding normal cells.

A large body of research has described stem cells (SCs) in normal tissues, which are capable of renewing themselves through asymmetrical cell division while simultaneously generating committed progenitor cells whose descendants may eventually differentiate and carry out tissue-specific functions. SCs have properties such as migration toward cancer cells, secretion of bioactive factors and immunosuppression which show the capability of stem cell (SC) therapy in targeted anti-cancer treatment and its application in the treatment of HNSCC. Because CSCs play an important role in tumour development, relapse and metastasis, newly developed molecular targeting of deregulated signalling elements in CS/progenitor cells, and their local microenvironment represents a new potential strategy for the development of more effective clinical treatments against aggressive cancer targeting CSC surface markers bringing great promise for cancer therapy. SCs engineered to stably express various cytotoxic agents decrease tumour volumes and extend survival in preclinical animal models.[4] This review discusses the types of SCs, the role of CSCs in the course and relapse of HNSCC, various surface markers for their identification, and SC-targeted therapy options for the treatment of HNSCC with a highlight on advantages, shortcomings, opportunities and challenges to SC therapy in HNSCC treatment and scope for future research.

TYPES OF STEM CELLS

SCs are defined by their ability to:

1) Self-renew indefinitely
2) Form single-cell-derived clonal cell populations
3) Differentiate into various cell types.

SCs can be broadly categorized as 'embryonic stem cells' (ESCs) or 'somatic stem cells' (SSCs). SSCs are also known as adult stem cells, which are generally multipotent and can differentiate into any cell type with a specific lineage, including neural stem cells (NSCs), mesenchymal stem cells (MSCs), haematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), whereas embryonic stem cells (ESCs) can form induced pluripotent stem cells (iPSCs). SCs implicated in HNSCC are tabulated further in Table 1.

CSCS IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

Various studies through the past many decades have concluded cancer cells as being 'transformed cells,' with a series of mutations, permitting them to self-renew, proliferate and form tumours.[5] Cancer cells may arise from

a. CSCs
b. Bacterial acquisition and hybridisation of the host's DNA
c. Embryonal rests
d. Maturation arrest
e. Dedifferentiation of mature cells
f. Mutations of SCs
g. Transformation of progenitor cells.

CSCs are isolated from patient tissues and cell lines of different cancer types. CSCs express stemness genes, self-renew, differentiate into other non-stem cancer cells and resist traditional cancer treatments. Traditional cancer therapies can kill non-stem cancer cells, but cannot eliminate CSCs. Tumours usually relapse when the remaining CSCs proliferate and differentiate. Therefore, targeting CSCs may solve clinical issues such as drug resistance and cancer recurrence.

The well-accepted concept states that for carcinogenesis to occur, more than one critical mutation (around 3–7) is required to bypass the DNA repair mechanism and acquire the ability of indefinite proliferation. A study using whole-genome sequencing found that normal people carry 'driver' mutations during the first decade of their life, the

Table 1: Types of stem cells in HNSCC

NSCs	NSCs are typified by the expression of nestin, Sox2 and other classic markers, together with expansion in culture media rich in epidermal and fibroblast growth factors. NSCs have the capability to self-renew and differentiate into the astrocytes, neurons or oligodendrocytes, and have been widely employed to treat brain, breast, prostate and lung tumours.
MSCs	MSCs are derived from the bone marrow and can differentiate into mesodermal cells, including cartilage, bones, adipose tissue, stroma, muscles, connective tissue, and tendon. MSCs are easily isolated and propagated *in vitro* and, like NSCs, are used widely in the treatment of different cancers.
HSCs	They are the most primitive of blood lineage cells, are predominantly found in the bone marrow and produce mature blood cells through the proliferation and differentiation of increasingly lineage-restricted progenitors.
EPCs	EPCs are the primary drivers of vascular regeneration. Asahara *et al*.[7] suggested the potential utility for EPCs in cancer therapy, following the transfection or coupling with antitumour drugs or angiogenesis inhibitors.
ESCs and iPSCs	Like pluripotent cells, ESCs can differentiate into all cell types, except those in the placenta, and are therefore used as gold standards in the evaluation of all pluripotent cells cultured in vitro. ESCs can be replaced by iPSCs reprogrammed from adult somatic cells (e.g. skin fibroblasts) through enforced expression of pluripotency factors because iPSCs establishment does not require the destruction of embryo. iPSCs are similar to ESCs, but lack immunogenic or ethical limitations, and hence are clinically more applicable.

burden of which increases with age.[6] After a few mutations in SCs and their transformation into cancer cells, they can become the origin or transmitter of cancer.

CSCs have greatly enhanced tumour-initiating potential as compared to other cells in cancer. They can also self-renew and generate non-CSC progeny (explaining the heterogenicity of the original tumour). CSCs show resistance to chemotherapy and radiotherapy, requiring a change in the current concept focused on the reduction of tumour mass. If these CSCs are not targeted during treatment, they can lead to tumour relapse, metastasis and worsening of prognosis.[8]

On realisation of the concept that tumourigenesis requires mutations in cells, Fearon and Vogelstein[9] developed the clonal evolution concept that explains the progression of a tumour towards a more aggressive one by the stepwise acquisition of mutations, that is, tumour cells can become CSCs with a sufficient accumulation of mutations. Theories conclude that CSCs can originate from normal SCs or progenitor cells by genetic alteration and dedifferentiation; gaining the features of CSCs. This can also result from the union of HSCs with a mutated somatic epithelial cell or from the dedifferentiation of a mature cell. Dedifferentiated somatic cells and cancer cells may undergo epithelial–mesenchymal transition to form CSCs. Cells comprising the vasculature, non-epithelial stromal cells and inflammatory cells also help in sustaining these CSCs.

CSCs differ from normal SCs by their indefinite replication ability, producing phenotypically diverse progeny, aneuploidy with chromosomal rearrangements and characteristic short telomeres (which is the hallmark of cancer).

CSC BIOMARKERS IN HNSCC

A cancer biomarker is a characteristic that is measured as an indicator of the risk of cancer, occurrence of cancer or patient outcome. These characteristics can be either molecular, cellular, physiologic or imaging-based. Biomarker testing in cancer involves profiling tumour or body fluids to detect changes in DNA, RNA, proteins or other biomolecules that provide information for cancer diagnosis, prognosis, precision medicine/guiding cancer treatment, predicting drug response or cancer monitoring.[10]

In cancer research and medicine, biomarkers are used in three primary ways.[11]

1. To help diagnose conditions, as in the case of identifying early-stage cancers (diagnostic)
2. To forecast how aggressive a condition is, as in the case of determining a patient's ability to fare in the absence of treatment (prognostic)
3. To predict how well a patient will respond to treatment (predictive).

The markers for the detection of HNSCC are enumerated as follows -

1. CD44

CD44, a cell-surface glycoprotein, functions as a receptor for hyaluronic acid and is involved in cell adhesion and migration.[12] Prince *et al*.[12] (2007) demonstrated that CD44 serves as a CSC marker in HNSCC. It has also been shown that $CD44^+$ cells express high levels of Bmi-1,[12] a self-renewal protein found in ESCs.[13]

2. ALDH

The aldehyde dehydrogenase (ALDH) family of enzymes are cytosolic isoenzymes that are responsible for oxidizing intracellular aldehydes and contributing to the oxidation of retinol to retinoic acid in early SC differentiation. Furthermore, the activity of the ALDH1 enzyme has been identified as being responsible for the resistance of progenitor cells to chemotherapeutic agents and can be used to select a highly enriched population of progenitor cells in the bone marrow and umbilical cord sources. Visus

et al.[14] further suggested that ALDH1A1 is a marker in HNSCC for distinguishing premalignant cells and is also an essential epitope for developing ALDH1A1-based vaccines for HNSCC therapy. Recent studies have shown that ALDH1 is a CSC marker and that its presence strongly correlates with tumour malignancy as well as self-renewal properties of SCs in different tumours, including breast cancer, hepatoma, colon cancer and lung cancer.

3. CD133

The transmembrane glycoprotein CD133 has also been investigated as a putative marker for CSCs.[12] In some HNSCC cell lines (e.g. hep-2), CD133 cells were found to have increased clonality when compared with CD133-cells.[12] Oral cancer stem-like cells from cell lines and primary tumours were found to have an increased expression of CD133 and displayed increased migration and tumourigenicity as compared with controls.[15]

4. Bmi-1

Bmi-1 is an epigenetic regulator, a stemness-related gene, which maintains the self-renewal ability of SCs by modulating the chromatin structure. It promotes cell proliferation and is also involved in carcinogenesis. In HNSCC, it is linked with self-renewal, colony formation, migration and invasion and is strongly associated with advanced stages, aggressive clinicopathological behaviour drug resistance and thus, poor prognosis.[16]

5. Krüppel-Like Factor 4 (KLF4)

Krüppel-like factor 4 transcription factor shows an inconsistent pattern in HNSCC, with the majority of samples from patients with HNSCC showing decreased expression. However, HNSCC with increased KLF4 expression is linked to low disease-specific survival, whereas its ectopic expression advances tumour progression. Paparella *et al*.,[16] in their study using a mouse model, showed that knockout of *KLF4* in the oral epithelium increases the chances of malignant OSCC lesions, hinting towards a probable tumour suppression role.

6. c-Met

c-Met is a tyrosine kinase receptor for hepatocyte growth factor (HGF) that has been reportedly linked to tumour invasion, metastasis and decreased survival in HNSCC.[16]

7. CD10

CD10 is a zinc-dependent metalloendoprotease, which is found in normal tissues, and has also been affiliated with tumour size, histological grade of malignancy, local recurrence and therapeutic resistance in HNSCC.[16]

8. SOX2

SOX2 has been linked to the process of tumourigenesis, and its upregulation has been reported in tumours of squamous lineage. In HNSCC, it confederates with cell proliferation, migration, invasion, anti-apoptosis, radio chemoresistance and thus, poor prognosis.[16]

9. OCT4

OCT4 is crucial for epithelial–mesenchymal transition and also has been linked to the oncogenic process. In OSCC, positive expression of this marker is observed in metastatic lymph nodes and recurrent tumours. Moreover, it is associated with poor survival in HNSCC and is contemplated as an independent prognostic marker for the same entity.[16]

10. NANOG

The expression of NANOG is amplified in HNSCC CSCs and is linked to tumour transformation, tumourigenicity and metastasis. It also corresponds with poor differentiation status, chemoresistance and thus, poor prognosis in HNSCC.[16]

SOX2, OCT4 and NANOG transcription factors act as regulators for self-renewal and maintenance of undifferentiated states in ESCs, and thus are classified as stemness markers.

STEM CELL-TARGETED THERAPY

Stromal environment and CSC niche play a key role in the behaviour of cancer cells and, hence, targeting the SCs niche directly can weaken the source of nutrition and change the essential signals needed by CSCs to proliferate. Tang *et al*.[17] suggested that targeting CSCs and their microenvironmental niche, which contributes to selfrenewal of these cells along with the reactive oxygen species status of these cells, and tweaking their intracellular milieu to facilitate apoptotic death signals over proliferative effects may facilitate a new prospective towards target therapy in cancer.

The SC theory of cancer suggests that malignant cells within a tumour are heterogeneous in their phenotypical and functional properties including differentiation, self-renewal and tumour-initiation capacities.

A number of preclinical studies have aimed at the elimination of CSCs. Recently, Kerk *et al*.[18] found a higher expression of 5T4, an oncofoetal antigen, in HNSCC SCs. This study analysed patient tissue arrays and found a correlation between 5T4 levels and lower overall survival. In a preclinical model, MEDI0641, a 5T4-inhibitor, reduced the CSC fraction and prevented local recurrence.

Sun *et al*.[19] reported a CSC-targeting potential for the c-Met inhibitor PF-2341066 and synergistic effects in combination with chemotherapy in HNSCC patient-derived xenograft models. The elimination of CSCs was achieved by the downregulation of the Wnt/β-catenin signalling pathway via the disruption of c-Met and frizzled class receptor 8 interaction.

There is an ongoing debate regarding the clinical applicability of natural compounds with CSC inhibition properties including 6-gingerol with Wnt/β-catenin targeting potential, β-carotene, which inhibits Oct4 as well as curcumin, cyclopamine or genistein targeting hedgehog and Notch signalling. Several studies have investigated their potential in HNSCC *in vitro*.[20] Potential targeting of CSCs can be realized in different fashions, including targeting of CSC-related molecules, interfering with the environment promoting CSC functions or inhibiting molecular pathways critical for CSC maintenance and survival.

The main three pathways are as follows:-

1. Targeting self-renewal pathways

One of the most promising strategies for targeting HNSCC CSCs is blocking the key self-renewal signalling cascades, such as those regulated by EGFR, NOTCH, WNT and SHH. It has been determined that gefitinib (a tyrosine kinase inhibitor) preferentially targets CSCs, eliminating tumour regrowth and increasing sensitivity to cisplatin in nasopharyngeal carcinoma. Moreover, blocking EGFR with gefitinib reduces the expression of c-MYC and NANOG, essential factors for reprogramming of iPSCs.[21]

Targeted therapy against these pathways that are deregulated in CSCs resulted in a mark reduction in tumourigenic potential.

Three pathways that can be targeted are as follows:-

A. The Wnt pathway

Suppression of the Wnt signalling inhibits the progression of OSCC. Micro RNAs have been shown to suppress tumour progression by regulating the Wnt signalling. Wnt signalling plays an important role in maintaining the pluripotency of human ESCs.[22]

B. The Hedgehog pathway

The activation of the Hedgehog pathway promotes angiogenesis in OSCC. The involvement of the Hedgehog pathway has been shown in angiogenesis by macrophages and endothelial cells. Hedgehog and TGF-β signalling is involved in bone invasion and destruction. The expression of *Gli2* is associated with bone invasion. *Gli3* knockdown in tongue squamous cell carcinoma (TSCC) cells has resulted in the downregulation of CSC markers such as *CD44*, *OCT-4* and *BMI-1* genes and a reduction in CSCs. Further, an increased expression of Gli1 has been shown in spheroid-forming cells in the TSCC cell line.[23]

C. The HGF/c-MET pathway

The HGF/c-MET pathway is involved in tumourigenesis. The binding of ligand HGF to the kinase receptor c-MET leads to the dimerisation of two subunits. The dimerisation results in the auto-phosphorylation of tyrosine residues in the cytoplasmic domain of the receptor, which then creates a docking site for various adaptor proteins that regulate pathways such as the PI3K/AKT pathway and Wnt pathway. HGF treatment has been shown to increase the expression of CSC markers and the sphere-forming ability of HNSCC cells, which were decreased upon *c-MET* knockdown.[24]

2. Targeting Metabolic and Cell Surface Markers

The markers used to identify and enrich CSCs may have potential as targets for HNSCC therapy. Among the first reports involving therapeutic targeting of CD44, a study by Damek-Poprawa *et al*.[25] investigated the effect of the re-conjugated U36 antibody against the splice variant CD44v6, which was well-tolerated and showed initial promise. Another study by Börjesson *et al*.[26] indicated that the anti-CD44v6 monoclonal antibody BIWA 4 (bivatuzumab) has antitumour effects, and disease stabilisation was observed in patients with recurrent locoregional and/or metastatic HNSCC.

3. Targeting Stem Cell Factors

Another potential therapeutic target to eradicate CSCs is the transcription factor NANOG. Targeting NANOG in combination with cisplatin suppressed SC properties of HNSCC cells and enhanced apoptosis and chemosensitivity.[27]

TREATMENT OPTIONS USING SCS

The main reasons for cancer treatment failure and relapse are cancer heterogenicity and chemoresistance. This heterogenicity is attributed to the presence of CSCs, which curtails the effectiveness of chemotherapy and radiotherapy. CSCs have a major role in chemoresistance because of their ability to generate multipotent or unipotent differentiated cells of different lineages in response to chemotherapeutic agents.[28] CSCs can induce the quiescent cell state, forging them resistant to chemo and radiotherapy. Therefore, targeting these CSCs in solid tumours becomes essential to increase the efficacy of treatment and prevent tumour recurrence and relapse.

Because CSCs can attract normal SCs, normal SCs can be potentially used to target CSCs in cancer therapy. Interactions between normal SCs and CSCs suppress tumour proliferation, angiogenesis, and metastasis and reduce inflammation and apoptosis.[4]

Targeting CSCs therapeutically is challenging because both bulk tumour cells and CSCs must be eliminated, potentially demanding a combination of drug therapies. Because CSCs are molecularly distinct from bulk tumour cells, one can target their activity by exploiting these molecular differences. For instance, cell surface marker expression could be used for antibody-directed therapy to target proteins such as CD133 and CD44.[29]

Due to their extravagant properties of differentiation, migration, immunosuppression, immunomodulation, cell proliferation, clonogenicity and ability to regulate and escape host innate and cellular immune pathways, sensitize resistant tumour cells, eliminate residual tumour-initiating cells and prevent disease relapse, SCs can be used to target CSCs in cancer therapy. They also have tumour tropic properties due to chemokine-cancer cell interactions, which are intervened due to intercommunication between chemokine receptors present on the surface of SCs and chemokines released by altered tissues, thus enabling them to migrate to cancer niches, providing them tumour-homing capability and making the targeting of tumour niches more precise. Various biomaterials such as degradable polylactide ethylene oxide fumarate (PLEOF) hydrogels can be employed for more pronounced and sustained release of chemokines.[30]

SCs can be modified as enzymes or prodrug therapy, secretory agents, viral therapy (oncolytic virus delivery at cancer site), nanoparticle carriers, regenerative medicine and immunotherapy or can be used to target CSCs or as anticancer drug screening. Most commonly used cells are NSC and MSC after certain modifications and tissue engineering techniques. The ability of MSCs to preferentially migrate towards local and disseminated malignant disease and their nonimmunogenic nature present them as the most attractive candidates for cell-based therapies in humans.[31]

ENZYMES/PRODRUG

SCs can be therapeutically engineered to express bioactive enzymes and chemokines that can generate cytotoxic products from nontoxic prodrugs.

Cytosine deaminase is a major enzyme currently used in enzyme/prodrug therapy. Cytosine deaminase converts the prodrug, 5-fluorocytosine, into the toxic variant, 5-fluorouracil.[4] The cell-targeted approach allows a locally high concentration of therapeutic agent to be delivered in the vicinity of tumour, causing it to reduce significantly in volume while producing less systemic toxicity.

MSCs engineered to co-express the prodrug converting enzyme, Herpes simplex virus thymidine kinase (HSV-TK) and a potent and secretable variant of tumour necrosis factor apoptosis-inducing ligand (S-TRAIL), induced caspase-mediated glioblastoma multiformae (GBM) cell death and showed selective MSC sensitisation to the prodrug ganciclovir. A significant decrease in tumour growth and a subsequent increase in survival were observed when mice bearing highly aggressive GBM were treated with MSCs co-expressing S-TRAIL and HSV-TK.[32]

Modified SCs can be targeted to cancerous niches and can be made to deliver exogenous enzymes that can activate the prodrug into cytotoxic products and kill the cancerous cells. Because the CSCs are used to deliver exogenous enzymes, the entire process can be precisely controlled in terms of location, timing and amount of drug delivered.[32]

Human MSCs have been engineered to express and provide targeted delivery of interferonβ (IFNβ), immunomodulatory cytokines such as interleukin (IL) 2, IL4, IL12, IL23, HSV-TK, TRAIL, metalloproteinases (PEX), including prodrug-activating enzymes (cytosine deaminase, carboxylesterase and thymidine kinase) to many types of tumours including GBM models. The administration of therapeutic MSCs has revealed a reduction of tumour growth, resulting in increased survival of GBM-bearing mice.[32,33]

NSCs and MSCs can deliver therapeutic genes to elicit a significant antitumour response in animal models of intracranial glioma, medulloblastoma, melanoma brain metastasis, disseminated neuroblastoma and breast cancer lung metastasis. Most studies reported a reduction in the tumour volume (up to 90%) and increased survival of tumour-bearing animals.[33]

Secretory agents

SCs can act as drug reservoirs and drug delivery agents due to their secretory actions such as secretion of CCL2/MCP-1 and also intrinsic antitumour properties by virtue of which they can alter the cancer cell phenotypes.[4]

SCs can function as *in situ* drug factories, secreting antitumour agents for an extended time, and overcoming various cancer therapy limitations, such as high systematic toxicity and short drug half-life. S-TRAIL is one of the

most widely used, secreted therapeutic agents and induces tumour cell apoptosis.[4]

SCs can also be modified to selectively deliver growth inhibitory proteins (e.g., IFN-β), rendering the microenvironment inhospitable to tumour growth.[4]

Transplanted NSCs have recently been recognized for their remarkable ability to migrate throughout CNS, become normal constituents of the host cytoarchitecture and disseminate bioactive molecules and retroviral vectors. The ability of NSCs to migrate expeditiously throughout a tumour mass and, presumably drawn by the degenerative or inflammatory environment created at the infiltrating tumour edge, to 'surround' the invading tumour border, all while continuing to express a bioactively relevant transgene.[34]

Viral therapy

Viral therapy oncolytic viruses (OVs), unlike traditional attenuated viruses, conditionally replicate in tumour cells. OVs have increased spread in the body and hide from the immune system. Virus delivery by MSCs is also a promising approach for targeted cancer therapy.

Aboody *et al*.[35] used a neural SC line carrying a *v-myc* gene and a gene for cytosine deaminase. These cells exhibit tropism to human glioma cells. When injected into mice with gliomas, they migrate to the site of the tumour, even when the mice are treated with steroids or radiation, as might be the case for human patients. Cytosine deaminase in the cells provides another anticancer weapon. This enzyme converts the prodrug 5-fluorocytosine to the toxic 5-fluorouracil,[4] delivering a high concentration of the therapeutic agent directly in and around the tumour, causing it to shrink significantly. This targeted cell-based approach to cancer therapy that concentrates the therapeutic agent in the vicinity of the tumour is expected to reduce toxicity to other tissues. Thus, a higher local dose is possible, potentially improving efficacy against the tumour.

Nanoparticle carriers

Failure of conventional therapies to target and eradicate micrometastatic lesions, distant tumour foci and inefficient dissemination in solid tumours can be overcome using SCs as nanoparticle (NP) delivery agents.

NP carriers delivery systems based on NP carriers often contain a high concentration of insoluble anti-carcinogenic/chemotherapeutic reagents for targeted delivery into tumours using conjugation/fusion of drugs to tumour-specific antibodies, encapsulation of tumour-specific antibodies, encapsulation of tumour-specific agents into liposomes and the use of genetically engineered stem/progenitor cells as vehicles. SCs can also reduce unrestricted uptake of NPs by mononuclear cells and protect therapeutic agents from host immunosurveillance and allow for sustained drug release. They can be easily manipulated with the addition of ligands to enhance NP permeability. MSC cell membranes can be loaded with doxorubicin-containing porous silica nanorattles for tumour-tropic therapy.[36] This approach increased and extended intratumoural drug distribution and promoted tumour cell apoptosis more than free drug or drug delivery systems using silica nanorattles alone. Thus, SCs-mediated NP-based drug delivery shows great promise in cancer treatments and warrants further investigation.[4] SCs-NP system can migrate through the interstitial barriers and can migrate, adhere, and engraft to the injured/affected tissue, showing tumour-homing ability.[37]

Immunotherapy

Immunotherapy can be used in the cure of haematological malignancies. SCs can be encoded with specific gene-encoding receptors such as chimeric antigen receptors and T-cell receptors, which are retained in T lymphocytes and can activate them, as well as directed against tumour-associated antigens.

Engineered SCs can also bring about apoptosis of CSCs by targeting various molecular pathways. The iPSCs can be used to screen new anticancer drugs and assess candidate antitumour drug toxicities.[4]

Autologous HSC transplantation is frequently used to rescue haematopoiesis after high-dose chemotherapy.[4]

Regenerative medicine

Due to the property of differentiation and self-renewal, SCs can be used to regenerate and repair tumour and treat injured (high-dose chemotherapy and radiotherapy, surgical) tissues.

Scaffold generation modality and iPSCs can be made to produce and differentiate respectively into various tissues to generate head and neck structures.

According to Pittenger *et al*.,[38] bone marrow-derived MSCs are now under consideration for the repair of the craniofacial bone and even the replacement or regeneration of oral tissues.

MSC-derived chondrocytes can be used for the reconstruction of orofacial cartilage structures, such

as temporomandibular joint and nasal cartilage. MSC-derived osteoblasts can be used for the regeneration of oral and craniofacial bones. MSC-derived myocytes can be used to treat muscular dystrophy and facial muscle atrophy.[39]

ADVANTAGES AND DISADVANTAGES OF STEM CELL THERAPY

The advantages and disadvantages of SCs are tabulated further in Table 2.

CONCLUSION

With an alarming rise in the number of new malignancies detected worldwide and fair success rates of current therapeutic strategies, a new approach to treating cancer that will help decrease mortality as well as morbidity of patients has come into the role.

SC therapy has unleashed new opportunities in the field of diagnosis, prognosis and prevention of cancer and its research, becoming potential milestones if elucidated more extensively. They have unique biological properties such as differentiation, migration, immunosuppression, immunomodulation, cell proliferation, clonogenicity and the ability to regulate and escape host innate and cellular immune pathways, sensitize resistant tumour cells, eliminate residual tumour-initiating cells and prevent disease relapse, due to which they can be used to target the CSCs in cancer therapy. They have also been used in viral therapy, immunotherapy, regenerative medicine and nanoparticle carrier systems, thus enhancing their arena of action and use.

Despite a large number of advantages, there are still some constraints and limitations linked to the use of SCs such as immune rejection of donor cells, oncogenic potential, toxicity of CSC-targeting agents, social and ethical concerns and funding limitations. We need to spur efforts to surmount and expedite the challenges associated with SCs to attain more predictable outcomes with SCs.

Abbreviations

ALDH	Aldehyde dehydrogenase
CSC	Cancer stem cell
EPC	Embryonic progenitor cell
ESC	Endothelial stem cell
GBM	Glioblastoma multiformae
HGF	Hepatocyte growth factor
HNSCC	Head and neck squamous cell carcinoma
HSC	Haematopoietic stem cell
HSV-TK	Herpes simplex virus thymidine kinase
IFNβ	Interferonβ
iPSC	Induced pluripotent stem cell
KLF4	Krüppel-like factor 4
MSC	Mesenchymal stem cell
NP	Nanoparticle
NSC	Neural stem cell
OSCC	Oral squamous cell carcinoma
OV	Oncolytic virus
SC	Stem cell
S-TRAIL	Secretable variant of tumour necrosis factor apoptosis-inducing ligand

Financial support and sponsorship

Nil.

Table 2: Advantages and disadvantages of stem cell therapy

ADVANTAGES	DISADVANTAGES
SCs can be used in the production of biologic regulators on industrial scale.[40]	Immune rejection of donor cells by the host immune system post-transplantation.[41]
Have both diagnostic and therapeutic potential.[42]	Donor SCs that manage to escape immune rejection may later become oncogenic because of their unlimited capacity to replicate.[42]
iPSCs and their derivatives have provided excellent *in vitro* models of disease processes.[42]	The use of SCs raises social and ethical concerns.[41]
Patient-specific iPSC models will serve as an invaluable tool for drug discovery and toxicology studies.[42]	Funding limitations.[41]
Therapeutic potential of these cells to regenerate functional tissue and replace damaged tissue has vast potential.[42]	Collection of SCs is difficult.[41]
SC-based therapies may enhance the body's own ability to repair itself.[42]	Existence of mobile CSCs might later induce proliferation and differentiation of CSCs, leading to both primary tumour recurrence and metastatic growth.
MSCs are used as a tool to treat degenerative changes in the joints and reconstruct oral tissues bones and cartilage, and are used in plastic surgeries, aesthetic medicine, cardiovascular diseases, endocrine and nervous system diseases, cell transplantation, and in the repair of damaged musculoskeletal tissues.[43]	Toxicity of CSC-targeting agents.
Anti-tumourigenic effects.[44]	Initial therapeutic attempts using either ESCs or iPSCs will require adjunctive immunosuppressive therapy. Immunosuppressive therapy, however, puts the patient at risk of infection as well as drug-specific adverse reactions.[42]
Inducing apoptosis and necrosis of tumour cells.[44]	
Low rejection rates of adult SCs.[41]	
Can be transformed into pluripotent SCs.[41]	
iPSCs are already powerful tools for modeling disease processes.[42]	

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Parkin D, Piñeros M, Znaor A, *et al*. Cancer statistics for the year 2020: An overview. Int J Cancer 2021;149:778-89.
2. Patel SS, Shah KA, Shah MJ, Kothari KC, Rawal RM. Cancer stem cells and stemness markers in oral squamous cell carcinomas. Asian Pac J Cancer Prev 2014;15:8549-56.
3. Mimeault M, Batra SK. Targeting of cancer stem/progenitor cells plus stem cell-based therapies: The ultimate hope for treating and curing aggressive and recurrent cancers. Panminerva Med 2008;50:3-18.
4. Zhang CL, Huang T, Wu BL, He WX, Liu D. Stem cells in cancer therapy: Opportunities and challenges. Oncotarget 2017;8:75756-66.
5. Yin W, Wang J, Jiang L, James Kang Y. Cancer and stem cells. Exp Biol Med (Maywood) 2021;246:1791-801.
6. Moore L, Leongamornlert D, Coorens THH, Sanders MA, Ellis P, Dentro SC, *et al*. The mutational landscape of normal human endometrial epithelium. Nature 2020;580:640-6.
7. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, *et al*. Isolation of putative progenitor endothelial cells for angiogenesis. Science 1997;275:964-7.
8. Kumar HA, Desai A, Mohiddin G, Mishra P, Bhattacharyya A, Nishat R. Cancer stem cells in head and neck squamous cell carcinoma. J Pharm Bioallied Sci 2023;15(Suppl 2):826-30.
9. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759–67.
10. Sarhadi VK, Armengol G. Molecular biomarkers in cancer. Biomolecules 2022;12:1021.
11. Biomarkers in Cancer: An Introductory Guide for Advocates. Research Advocacy Network; 2010.
12. Prince ME, Sivanandan R, Kaczorowski A, Wolf GT, Kaplan MJ, Dalerba P, *et al*. Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. Proc Natl Acad Sci U S A 2007;104:973-8.
13. Bracken-Roche D, Bell E, Macdonald ME, Racine E. The concept of 'vulnerability' in research ethics: An in-depth analysis of policies and guidelines. Health Res Policy Syst 2017;15:8.
14. Visus C, Ito D, Amoscato A, Maciejewska-Franczak M, Abdelsalem A, Dhir R, *et al*. Identification of human aldehyde dehydrogenase 1 family member A1 as a novel CD8+T-cell-defined tumor antigen in squamous cell carcinoma of the head and neck. Cancer Res 2007;67:10538-45.
15. Chiou J, Geusz RJ, Okino ML, Han JY, Miller M, Melton R, *et al*. Interpreting type 1 diabetes risk with genetics and single-cell epigenomics. Nature 2021;594:398-402.
16. Paparella ML, Abrigo M, Bal de Kier Joffe, Raimondi AR. Oral-specific ablation of Klf4 disrupts epithelial terminal differentiation and increases premalignant lesions and carcinomas upon chemical carcinogenesis. J Oral Patol Med 2015;44:801-9.
17. Tang C, Ang BT, Pervaiz S. Cancer stem cell: Target for anti cancer therapy. FASEB J 2007;21:3777-85.
18. Kerk SA, Finkel KA, Pearson AT, Warner KA, Zhang Z, Nör F, *et al*. 5T4-targeted therapy ablates cancer stem cells and prevents recurrence of head and neck squamous cell carcinoma. Clin Cancer Res 2017;23:2516-27.
19. Sun S, Liu S, Duan SZ, Zhang L, Zhou H, Hu Y, *et al*. Targeting the c-Met/FZD8 signaling axis eliminates patient-derived cancer stem-like cells in head and neck squamous carcinomas. Cancer Res 2014;74:7546–59.
20. Borges GA, Rego DF, Assad DX, Coletta RD, De Luca Canto G, Guerra EN. *In vivo* and *in vitro* effects of curcumin on head and neck carcinoma: A systematic review. J Oral Pathol Med 2017;46:3–20.
21. Ma L, Zhang G, Miao XB, Deng XB, Wu Y, Liu Y, *et al*. Cancer stem-like cell properties are regulated by EGFR/AKT/β-catenin signaling and preferentially inhibited by gefitinib in nasopharyngeal carcinoma. FEBS J 2013;280:2027-41.
22. Joshi P, Waghmare S. Molecular signaling in cancer stem cells of tongue squamous cell carcinoma: Therapeutic implications and challenges. World J Stem Cells 2023;15:438-52.
23. Essid N, Chambard JC, Elgaaïed AB. Induction of epithelial-mesenchymal transition (EMT) and Gli1 expression in head and neck squamous cell carcinoma (HNSCC) spheroid cultures. Bosn J Basic Med Sci 2018;18:336-46.
24. Zhang H, Feng Q, Chen WD, Wang YD. HGF/c-MET: A promising therapeutic target in the digestive system cancers. Int J Mol Sci 2018;19:3295.
25. Damek-Poprawa M, Volgina A, Korostoff J, Sollecito TP, Brose MS, O'Malley BW Jr, *et al*. Targeted inhibition of CD133+cells in oral cancer cell lines. J Dent Res 2011;90:638-45.
26. Börjesson PK, Postema EJ, Roos JC, Colnot DR, Marres HA, van Schie MH, *et al*. Phase I therapy study with (186) Re-labeled humanized monoclonal antibody BIWA 4 (bivatuzumab) in patients with head and neck squamous cell carcinoma. Clin Cancer Res 2003;9:3961S-72S.
27. Huang CE, Yu CC, Hu FW, Chou MY, Tsai LL. Enhanced chemosensitivity by targeting Nanog in head and neck squamous cell carcinomas. Int J Mol Sci 2014;15:14935–48.
28. Trédan O, Galmarini CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst 2007;99:1441-54.
29. Singh A, Settleman J. EMT, cancer stem cells and drug resistance: An emerging axis of evil in the war on cancer. Oncogene 2010;29:4741-51.
30. He X, Ma J, Jabbari E. Migration of marrow stromal cells in response to sustained release of stromal-derived factor-1alpha from poly (lactide ethylene oxide fumarate) hydrogels. Int J Pharm 2010;390:107-16.
31. Shah K. Mesenchymal stem cells engineered for cancer therapy. Adv Drug Deliv Rev 2012;64:739-48.
32. Martinez-Quintanilla J, Bhere D, Heidari P, He D, Mahmood U, Shah K. Therapeutic efficacy and fate of bimodal engineered stem cells in malignant brain tumors. Stem Cells 2013;31:1706-14.
33. Aboody KS, Najbauer J, Danks MK. Erratum. Stem and progenitor cell-mediated tumor selective gene therapy. Gene Ther 2008;15:1072.
34. Aboody KS, Brown A, Rainov NG, Bower KA, Liu S, Yang W, *et al*. Neural stem cells display extensive tropism for pathology in adult brain: Evidence from intracranial gliomas. Proc Natl Acad Sci U S A 2000;97:12846-51.
35. Aboody KS, Najbauer J, Metz M, Apuzzo M, Gutova M, Annala A, *et al*. Neural stem cell–mediated enzyme/prodrug therapy for glioma: Preclinical studies. Sci Transl Med 2013;184:184ra59. doi: 10.1126/scitranslmed. 3005365.
36. Li L, Guan Y, Liu H, Hao N, Liu T, Meng X, *et al*. Silica nanorattle-doxorubicin-anchored mesenchymal stem cells for tumor-tropic therapy. ACS Nano 2011;5:7462-70.
37. Musial-Wysocka A, Kot M, Majka M. The pros and cons of mesenchymal stem cell-based therapies. Cell Transplant 2019;28:801-12.
38. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, *et al*. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143-7.
39. Rai S, Kaur M, Kaur S. Applications of stem cells in interdisciplinary dentistry and beyond: An overview. Ann Med Health Sci Res 2013;3:245-54.
40. Wang JC, Dick JE. Cancer stem cells: Lessons from leukemia. Trends Cell Biol 2005;15:494-501.
41. Lohmor S, Verma R, Malik V, Kaushik D. Current status of regulatory perspectives on stem cell therapy in India. Biol Lett 2020;7:176-82.
42. Leventhal A, Chen G, Negro A, Boehm M. The benefits and risks of stem cell technology. Oral Dis 2012;18:217-22.
43. Murphy MB, Moncivais K, Caplan AI. Mesenchymal stem cells: Environmentally responsive therapeutics for regenerative medicine. Exp Mol Med 2013;45:e54.
44. Bruno S, Collino F, Iavello A, Camussi G. Effects of mesenchymal stromal cell-derived extracellular vesicles on tumor growth. Front Immunol 2014;5:382.