ROLE OF CANCER STEM CELLS IN RADIORESISTANCE OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

Abstract

Cancer stem cells (CSCs) are incredibly uncommon immortal cells that can be self-renewed by dividing and give rise to a wide variety of tumor-initiating cell types. Additionally, it is demonstrated that CSCs play a crucial role in metastatic spread and cell proliferation. Indisputable data reveals that cancer stem cells (CSCs) may be responsible for tumour recurrence if they are not eliminated by radiotherapy or radio-chemotherapy, two common modern treatments. Locally advanced head and neck squamous cell carcinoma (HNSCC), Despite recently made improvements in therapeutic methods and understanding of the molecular pathophysiology, continues to have a poor prognosis. Typically, CSCs are resistant to chemotherapy and radiation treatment, remaining CSCs that are still present after treatment may be able to survive and encourage cancer recurrence and resistance to treatments. In this review we address the role of CSCs and its mechanism in the resistance to therapy.

Authors

Dr. Priya Devi
Junior Resident
Department of Oral pathology & Microbiology
King George's Medical University
Lucknow, Uttar Pradesh, India
priyasandhu90413@gmail.com

Dr. Sharon John
Senior Resident
Department of Oral pathology & Microbiology
King George's Medical University
Lucknow, Uttar Pradesh, India
sharonjohn2540@gmail.com

Dr. Ayushi Jain
Junior Resident
Department of Oral pathology & Microbiology
King George's Medical University
Lucknow, Uttar Pradesh, India
ayushijain78656@gmail.com

Dr. Shalini Gupta
Professor and Head
Department of Oral pathology & Microbiology
King George's Medical University
Lucknow, Uttar Pradesh, India
dr.shalni@gmail.com

I. INTRODUCTION

Worldwide, head and neck squamous cell carcinoma (HNSCC) diagnoses total about 600,000 cases per year [1]. Although HNSCC is highly treatable in its early stages, 60% of patients receive a diagnosis of loco-regionally advanced illness (stage III–IV), which is linked to a poor prognosis. An improved outcome and organ preservation are made possible by intensified radiation plans and combination treatment strategies for advanced illness care. Persuasive evidence suggests that a population of so-called cancer stem cells (CSCs), which are in charge of tumour growth, dispersal, and relapse, maintains many malignancies. Recent evidence in various cancers that they can withstand traditional therapies, including ionising radiation, has given the CSC notion a higher level of prominence in cancer therapy. There is convincing evidence that a population of so-called cancer stem cells (CSCs), which are in charge of tumour growth, dispersal, and relapse, maintains a large number of tumours. Clinical and experimental data imply that CSC-related tumour characteristics, such as the number of CSCs present before to treatment and their innate radiosensitivity, may affect the response to radiation and radiochemotherapy in HNSCC [2].

II. CANCER STEM CELLS ORIGIN

Progenitor cells, which can divide into specialised or differentiated cells that perform the many activities of the body, are created from a variety of stem cell types. There is disagreement whether if CSCs originate from progenitor cells, stem cells, or differentiated cells. The traditional CSC model (hierarchical) and the clonal evolution model are currently the two main theories widely recognised for explaining the origin of cancer. In clonal evolution model, genetic mutations develop over time, and potentially any cell could be capable of causing cancer [3]. Tumours are arranged hierarchically in accordance with the CSC concept, with tumorigenic CSC at the top that divide asymmetrically to produce additional CSC as well as differentiated non-tumorigenic progenies. The possibility of bidirectional differentiation makes the CSC theory even more complex. In order to replenish depleted stem cells, differentiated non-tumorigenic tumour cells may undergo re-differentiation under the guidance of niche signals. The clonal evolution model and the CSC hypothesis may not be mutually exclusive, data support that the CSC theory with its hierarchical organisation of malignancies is much more convincing [4].

III. CANCER STEM CELLS IDENTIFICATION IN HNSCC

The production of particular cell surface antigens that promote the enrichment of cells with CSC characteristics has been by far the most popular technique for identifying CSCs. Many of these antigens were initially chosen as targets because endogenous stem cells are known to express them. Various biomarkers have been used to identify CSCs in human malignancies. Combining certain biomarkers, which are mostly found on the cell surface, allows for the separation of CSCs. Fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting are the two main methods of separation (MACS) The most used method for cell separation is now FACS. It can sort many biomarkers simultaneously, is very pure, and has good specificity. [5]. While numerous studies have discovered CSC markers in a wide range of solid tumours, HNSCC has seen comparatively little research on these markers. We will outline a couple of the validated markers for locating CSCs in HNSCC (Table 1).

Table 1: Various CSC markers with their description and role in HNSCC

CD133	Glycoprotein found on the protrusions of cell membranes.	Increased clonogenicity, tumor sphere formation, and tumorigenicity	[6]
CD44	Cell surface glycoprotein, aids in cell motility and adhesion	Possess the ability to self-renew, initiate, progress, invade, spread, cause a tumour to recur, and be resistant to chemotherapy and radiotherapy	[7]
Aldehyde Dehydrogenase Activity (ALDH)	Cytosolic isoenzymes, expressed in many stem and progenitor cells.	Metastasis, Tumourigenesis, and chemoresistance.	[8]
Side Population	Subpopulations of Hoechst 33342 dye resistant cells.	Chemoresistant, tumourigenic and have demonstrated self-renewal in vivo	[9]
Glucose regulated protein 78 (GRP78)	A chaperone protein found in endoplasmic reticulum	Reduction of GRP78 decreases tumorigenicity & self-renewal.	[10]
c-Met	Tyrosine kinase receptor for hepatocyte growth factor (HGF),	Tumour invasion, metastasis & decreased survival.	[11]

IV. MECHANISM OF RADIATION RESISTANCE IN HNSCC

The amount of radiation needed to totally eradicate a tumour, while all other confounding factors are kept constant, has an inverse relationship with the logarithm of the number of CSCs, suggesting that with the same irradiation dosage, tumours with fewer CSCs exhibit higher local control rates than tumours with more CSCs. There is a tumour volume dependency of the curability of malignancies in experimental and clinical data since the CSCs number is projected to increase with tumour volume [12]. In addition to serving as a model of disease development and metastasis, CSCs have significant treatment-related ramifications. The CSC hypothesis contends that effective cancer treatment can only be achieved by eradicating CSCs, whereas current chemotherapy and radiation treatments for

HNSCC concentrate on indiscriminate cytoreduction. However, there is strong evidence that CSCs are naturally resistant to drugs and radiation, which makes most conventional therapy ineffective and accounts for tumour recurrence despite dramatic tumour volume reductions. Different mechanisms underlie resistance. Radiation resistance is explained by accelerated DNA repair, in contrast to chemotherapy resistance, which is often associated with improved drug transport and metabolism. Possible treatment strategies include focusing on cancer stem cells, employing antiangiogenic medications, and encouraging CSC differentiation and maturation. Many efforts are being made to comprehend the molecular pathways unique to the pathobiology of CSC, which will enable specialised and focused treatment [13]. CSC radioresistance can be attributed to several factors as depicted in figure 1.

Figure 1: CSC radioresistance can be attributed to several factors (1) Apoptosis (2) Low Reactive Oxygen Species levels (3) Activation of DNA Repair mechanisms (4) cell cycle shutdown (5) Activation of Signalling pathways (6) Autophagy

1. **DNA Damage and Repair Induced by Radiation in Radioresistance:** In contrast to non-CSCs, key mechanism of radioresistance in CSCs appears to be connected to their improved capacity for DNA repair, ROS defences, and self-renewal potential. Double-strand breaks (DSBs) in DNA are caused by radioactive substances and ionising radiation (IR), and they typically result in DNA damage reactions (DDR). Irradiated cells experience the so-called mitotic crisis, a significant cell death mechanism for irradiation-induced DNA damage, when the DDR is unable to effectively repair the DSBs. The radioresistance of CSCs, which was first seen in glioblastoma multiforme (GBM) and breast cancer, appears to be linked to a greater capacity to neutralise free radicals produced in response to radiation as well as to variations in the processing and repair of DNA DSBs.

   Eukaryotes have acquired the natural capacity to repair DNA through evolution. The main routes for repairing DSBs are homologous recombination (HR) and nonhomologous end joining (NHEJ). To repair DSBs, HR needs sister chromatids' homologous DNA sequences. HR is consequently limited to cell cycle stages where sister chromatids are present (late S to G2 phases) [14]. NHEJ, on the other hand, is a promiscuous repair method that ligates two damaged ends without the need for sequence homology. As a result, NHEJ happens throughout the entire cell cycle. NHEJ frequently contains base deletions and insertions and is more error-prone than HR.

The quantity of DNA damage generated inside the cell and the capacity of the cell to activate repair mechanisms through DNA-damage response (DDR) pathways determine radiation sensitivity [15]. Cells cannot divide as a result of the failure of DDR activation and DNA repair, and instead succumb through processes such as necrosis, autophagy, apoptosis, mitotic catastrophe, or senescence [16]. Cancer cells that are radioresistant are more likely to increase the DDR rate. NHEJ is the primary radiation-induced DSB repair pathway, as was before mentioned. Radioresistance in HNSCC is linked to a number of NHEJ-related proteins [17].

2. **Effect of Reactive Oxygen Species (ROS) in Radioresistance:** The formation of free radicals, particularly the chemically reactive byproducts of oxygen metabolism known as reactive oxygen species, is one of the principal causes of radiation-induced cell death in traditional photon radiotherapy [18]. These metabolites participate in signalling events that control several cellular activities, including differentiation, proliferation, autophagy, and survival, under physiological settings [19]. However, if ROS generation exceeds the antioxidant capacity of the cell, it could result in irreversible oxidative stress and cell death [20]. Scavenging molecules including glutathione, thioredoxin, catalase, peroxidase, dismutase, and superoxide maintain the physiological ROS level. Additionally, a sufficient DDR response can decrease the negative effects of ROS. Either a very efficient ROS scavenging mechanism or the normal lower ROS levels in CSC populations may be responsible for the strong resilience of CSC populations to genotoxic stress documented for different tumour types. [21-23].

3. **Effect Of Extrinsic Microenvironmental Stimuli in Radioresistance:** Numerous external microenvironmental factors closely control the fate of CSCs in physiological situations and also while undergoing treatment, in addition to the internal processes governing CSC radioresistance that have been previously characterised [24, 25]. In a tumour, CSCs can live in several niches that can dynamically vary during tumour development and treatment, including hypoxic, perivascular, and invasive tumour regions [26,27]. Extracellular matrix (ECM) components, different soluble components and direct cell-cell interactions via cell surface chemicals define the CSC niche. A niche occupied by CSCs may determine its self-renewal, differentiation and resistance to treatment depending on oxygen tension. By producing fewer ROS and activating the hypoxia-inducible factor (HIF) signalling pathway than normoxic cells, CSCs in the hypoxic niche can be partially shielded from radiation damage [28-30]. To activate pro-survival developmental pathways i.e Wingless, INT-1 (WNT), Hedgehog, Notch, transcription factors HIF-1 and HIF-2 regulate gene transcription at Hypoxia responsive elements (HREs) [31- 33]. In addition to being related with resistance to radiation and faster CSC repopulation during or after treatment, activation of the signalling pathways are crucial for CSC maintenance [34-37].

V. CURRENT APPROACHES TO TARGET CSC IN HNSCC

While the CSC hypothesis contends that eliminating CSCs is the only effective approach to cure cancer, existing chemotherapy and radiation treatments for HNSCC do indeed aim towards indiscriminate cytoreduction. Thus, in HNSCC, substantial tumour volume reductions are insufficient to halt tumour recurrence. Therefore, CSCs are targeted in different ways. Different approaches to target CSCs are listed in Table 2.

Table 2: Approaches to target CSCs in HNSCC

Approaches to target CSCs in HNSCC	**Role in HNSCC**		**References**
1.Target different signalling pathways	Notch	Inhibition of NOTCH1 is able to repress CSC function & tumor growth and	[38]
	Wnt	Promote growth and survival, inhibit apoptosis	[39]
	Sonic Hedgehog (SHH)	Blockage of this pathway leads to inhibition of tumor growth and angiogenesis	[40]
	EGFR, TGF β	Triggers activation of an intracellular signaling cascade to control cell growth, differentiation, and survival. Elevated levels shows increased resistance to treatment and poor clinical outcome.	[41]
2. Targeting vascular niche	Niche offers the necessary conditions for self-renewal of cancer stem cell and maintenance		[42]
3. Target ROS status	Lower ROS levels in CSCs are associated with increased expression of free radical scavenging systems, overcoming low ROS levels within CSCs may be a useful method		
4. Inhibiting EMT	High expression of EMT-related genes in metastatic cell lines of HNSCC. Aberrant regulation of EMT transcription factors induces cancer cell plasticity and promote tumor initiation and metastatic spread.		[43]

Targeted CSC therapy has shown promising outcomes by focusing on different signalling pathways implicated in CSC development, such as Notch, Wnt, and Hedgehog (Figure 2). Drugs that target the pathways in CSC development have been developed by a large number of pharmaceutical companies. Some of the clinical trials on CSC in HNSCC is listed in Table 3.

Courtesy: The clinical trial information was accessed via https://clinicaltrials.gov with National Clinical Trial Number (NCT Number).
*STAT3 - Signal Transducer and Activator of Transcription

It has also been proposed that altering the intracellular environment of CSCs in HNSCC to target their ROS status will also result in targeted therapy that favours apoptotic death signals over proliferative ones [44].

According to Krishnamurthy et al, targeting CSCs directly or through their niche might result in a more effective treatment for HNSCC. The niche offers the necessary conditions for the self-renewal of cancer stem cell and maintenance, activating vital signalling pathways inside CSCs and trigger the production of substances that encourage angiogenesis and CSC growth in long term. It has been demonstrated that CSCs and angiogenesis interact in a "vascular niche". Therefore, it is crucial to concentrate on the "vascular niche" when treating HNSCC [45].

Epithelial mesenchymal transition (EMT) is the process through which polarised epithelial cells take on the characteristics of mesenchymal cells, which are known for their increased motility and invasiveness. Interaction of HNSCC cells with other cells in the tumour microenvironment gives them stem cell characteristics. Inhibiting EMT by preventing the communication between tumour and stromal cells could be a therapeutic approach for HNSCC.

Table 3: Clinical trials on CSCs in HNSCC

Molecule	**Function on**	**Phase/clinical trials**	**NCT Number**
IPI-926 & Cetuximab	Hedgehog Inhibitor	Phase 1	NCT01255800
Abemaciclib	Immune Modulation	Phase 2	NCT04169074
STAT* 3 DECOY	Targeting STAT3	Early Phase 1	NCT00696176
GX-051	Immune Modulation	Phase 1	NCT02079324

The role of CSC in the development of diseases has been better understood as a result of recent developments in molecular methods. A novel technique to fighting cancer that would aid in reducing patient mortality as well as morbidity must be quickly addressed. There is substantial evidence of a radiation-resistant tumour subpopulation that is additionally shielded by its surroundings and has improved DNA damage repair, decreased ROS, and higher survival signalling. Based on the most recent research on cancer treatment, we suggest a multi-strategic approach that might be more successful than conventional therapy, which

has not been able to reduce the morbidity and death of patients with HNSCC. The proposed multi-strategic approach that has been suggested combines conventional therapy, which might enable tumour debulking, and stem cell focused therapy, which could also prevent metastasis and recurrence, centres on targeting CSCs as its primary strategy.

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