

## REVIEW ARTICLE

## Trending Speculations of Tumor-Initiating Cells in Squamous Cell Cancers of Head and Neck

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Tumor-initiating cells are a diminutive subpopulation of stem cells that have ability of long term self-renewal and generation of varied traits of tumor cell population. Understanding the concept of tumor-initiating cells may have a great implicative intimation for our comprehension of cancer pathobiology and for the delineation of new therapies directed towards these stem cells. The present review is an endeavor to conceptualize the role of tumor-initiating cells in the Squamous Cell Cancers (SCC) of head and neck, their role in tumorigenesis and the possible supplementary approach in the latest treatment modalities.

**Keywords:** Tumor-initiating cells, Squamous cell cancer of head and neck, Malignancy, Undifferentiated cell

The worldwide increment in rate and mortality concerned with Squamous Cell Cancer (SCC) of the Head and Neck has increased endeavors in the field of research relating to tumor science and therapeutics. SCC of the Head and Neck is a standout amongst the most pervasive sorts of danger around the world. The mortality due to SCC of the Head and Neck mostly occurs by local recurrences and cervical lymph node metastasis and infrequently by distant organ metastasis. Various investigations into the malignancy therapeutics have helped in focusing on pathways that seem to contribute to tumorigenesis, and metastasis with more desirable effects and

less undesirable side impacts. Tumor-initiating cells have been distinguished in various solid organ malignancies, including Central Nervous System (CNS), pancreas, lung, colon, and lately in SCC of the Head and Neck after their first proposal in leukemic stem cells in the 1990s (1-6).

The generally agreed meaning of a tumor-initiating cell (also known as cancer stem cell) is a cell inside a tumor that has the ability to self-renew and to regenerate new tumors that consist of all clonally-derived cell types present in the parental tumor (7). This review is based on the speculations relating to the stem cells of cancer, specifically the tumor-initiating cell. The genesis of these cells, their part in malignancy progression and metastasis, and conceivable treatment modalities with special reference to SCC of the Head and Neck are highlighted in this review.

Different types of undifferentiated cells develop into the adult stem cells which can later divide into differentiated cells that complete a particular function of the body. It is dubious with reference to whether tumor-initiating cells emerge from undifferentiated cells, adult stem cells, or differentiated cells in an adult tissue. The issue is right now under argument and the speculations in the inception of tumor-initiating cells are displayed as under.

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### **Speculation no. 1: Tumor-initiating cells emerge from undifferentiated cells**

It has been speculated that the constrained life expectancy of a differentiated cell makes it more averse to live sufficiently long to undergo the multiple changes essential for tumor arrangement and metastasis. In this situation, tumor cells use the existing undifferentiated cell administrative pathways to advance their self-renewability. This ability to self-renew gives undifferentiated cells long life expectancies relative to those of progenitor and differentiated cells (8, 9).

### **Speculation no. 2: Tumor-initiating cells emerge from adult stem cells**

The quantity of adult stem cell is more inexhaustible in a fully developed tissue than are the undifferentiated cells. In spite of this, they hold a partial limit with regards to self-renewal. This property, when considered with their plenitude relative to undifferentiated cells in a fully developed tissue, frames the premise of speculation proposing that adult stem cells are a source of tumor-initiating cells (10, 11).

### **Speculation no. 3: Tumor-initiating cells emerge from differentiated cells**

It is proposed that tumor-initiating cells could emerge from differentiated cells that possibly dedifferentiate to turn into a distinctly more undifferentiated stem cell. In this situation, the imperative oncogenic hereditary changes would need to drive the dedifferentiation step and later ensure the self-renewability of the multiplying cells. This concept leaves open the likelihood that a generally huge populace of cells in the tissue could have tumorigenic potential; a little subset of these would really start the tumor. Particular components to choose which cells would dedifferentiate have not been proposed. Regardless, if a tissue contains an adequate populace of differentiated cells, the laws of likelihood demonstrate that a small portion of them could on a fundamental level, undergo the process necessary for de-differentiation (9). The part of EMT in SCC of the Head and Neck has now been adequately recognized and accepted. Initiation of Epithelial-mesenchymal Transition (EMT) in differentiated human epithelial cells leads to the acquisition of undifferentiated cell-like phenotype and development of tumor-initiating cells (12-14).

### **The role of tumor-initiating cells in tumor progression and metastasis**

A traditional concept, called the "the epigenetic progenitor origin of human cancer" characterized malignancy as a proliferative disease outsourcing from transformed tumor cells that contribute to the tumorigenic pursuit of all malignant cells inside a tumor. A large portion of the ideas in carcinogenesis and the treatment of tumor were predicated on such old malignancy concepts. As a result, therefore, it has had the greatest influence on the development of subsisting therapeutic strategies and biochemical malignancy markers so far, but it does not expound some fundamental facts about cancer cells like the diversity observed in a solitary cluster of cancer cells (15). Likewise, the premise of treatment based on this concept has not demonstrated to be useful till now. The stem cell theory of cancer is another characterizing concept for tumorigenesis which considers malignancy as an undifferentiated cell disease. It advocates that malignant undifferentiated cells have a crucial role to play in tumorigenesis (16). Undifferentiated cells at the highest point of their order have the ability to experience self-regeneration and can possibly separate into various sorts of cells in a particular genealogy (17, 18). The present concept of tumorigenesis avails to address most of the constraints of traditional malignancy model. Many researchers now consider that stem cell theory of cancer has a role in characterizing the procedure of tumorigenesis. Based on our review of sundry studies, we consider stem cell theory of cancer as more paramount for further discussion of the tumor-initiating cells concept.

The survival of an undifferentiated cell is to a great extent subordinate on the particular and specific "local microenvironment". The local microenvironment is made out of heterogeneous populaces including undifferentiated cells and adjacent differentiated cells that control basic inherent elements important in deciding the fate of undifferentiated cells. These basic elements include the stromal support cells, dissolvable factors, extracellular framework proteins, and blood vessels. The undifferentiated cells in the microenvironment maintain their distinctive stem cell properties like the property of self-renewal and primitiveness (19, 20). A comparable kind of microenvironment is essential for the survival of tumor-initiating cells. Factors such as inflammation, EMT, hypoxia, and angiogenesis occurring in tumor-initiating cells microenvironment assists to manage their lethal populace (20, 21).

Metastasis is an involute, multistep process that involves a concrete sequence of events; namely, malignant

cells must escape from the pristine tumor, migrate through the blood or lymph to a contemporary site, adhere to the contemporary site, move from the circulation into the local tissue, form micrometastases, develop a blood supply, and grow to develop an macroscopic and clinically pertinent metastases (22-24). Few scientists have proposed that tumor-initiating cells might be the miniature subsets of malignant cells that drive the spread of disease to the inaccessible organs (8, 25). In research based on the observations made in the human colorectal malignancy, an idea of migratory phenotype of cancer stem cells was presented. The sign of this concept is the presence of mobile malignant stem cells, which momentarily creates from stationary malignant stem cells by joining two unequivocal components: the ability to self-renew and differentiate into different tumor cell types and Epithelial-Mesenchymal Transition (EMT). Attributable to the property of mobility, these migratory phenotype of cancer cells can scatter through different entries to favored "local environment" at an inaccessible site which bolsters development and provides sustenance to these relocated cells. Changes in the microenvironment that encompass these cells, for example, inflammation and hormonal status, may later instigate repeated division and differentiation (Mesenchymal-Epithelial Transition) of dispersed malignant stem cells, prompting to both essential tumor recurrence and metastatic development (26). As of late in view of different molecular research, the idea of migrating cancer stem cell was demonstrated to hold importance even in SCC of Head and Neck (27).

### Identification of tumor-initiating cells

While a large number of studies have distinguished tumor-initiating cells markers over an assortment of solid malignancies, moderately few of these markers have been contemplated in SCC of Head and Neck. We will depict few of the demonstrated strategies by which malignant stem cells in SCC of Head and Neck can be distinguished. By a wide margin, the most well-known technique for recognizing tumor-initiating cells has depended on the increased expression of particular cell surface antigens that improve for cells with malignant stem cells properties. A significant number of these antigens were identified due to their known expression on endogenous stem cells.

#### CD133

A transmembrane glycoprotein localized on the cell surface is supposedly the malignant stem cell marker for various epithelial malignancies including colorectal, cere-

brum, prostate, breasts and lung (28-31). In SCC of Head and Neck cell lines, CD133<sup>hi</sup> cells display increased clonogenicity, tumorsphere formation and tumorigenicity in xenograft models when compared to their CD133<sup>low</sup> counterparts (32, 33).

#### CD44

It is a huge malignant stem cell marker that takes part in cell adhesion and migration. It is a known receptor for hyaluronic acid and interfaces with different organic molecules, for example, matrix metalloproteases (34, 35). It has been distinguished as a malignant stem cell marker in multiple cancers including the breast and colon cancer (36). Different researchers have now set up the role of CD44 positive cells as a malignant stem cell marker in SCC of Head and Neck (37-39).

#### Aldehyde Dehydrogenase

The aldehyde dehydrogenase family (ALDH) is a group of cytosolic isoenzymes which are exceptionally expressed in numerous stem and progenitor cells. ALDH detoxifies intracellular aldehydes through oxidation and probably have a role in the differentiation of stem cells through the oxidation of retinoic acid (40-42). Likewise, with CD44, the lead for researching ALDH as a marker for tumor-initiating cells in SCC of Head and Neck took after recognizable proof in other solid cancers, for example, breasts, colon, liver, and lung tumors (43-46). Numerous research in SCC of Head and Neck have demonstrated the part of ALDH1+ cells in tumorigenesis, metastasis, and chemoresistance in cancers of head and neck (40, 41, 47, 48).

#### ABCB5 expression

The novel human ATP-binding cassette (ABC) transporter ABCB5 (subfamily B [MDR/TAP] member 5) acts as an energy-dependent drug efflux transporter and marks tumor cells of a putative cancer stem cell compartment. ABCB5 acts as a multifunctional efflux transporter in tumor-initiating cells leading to increased survival and tumor relapse in SCC of Head and Neck. High expression of ABCB5 can be considered as an independent prognostic factor for CD44 tumor-initiating cells of SCC of Head and Neck (49).

#### Side population cells

A specific population of stem cells holding the ability to extrude dye like Hoechst 33342 is referred to as side population cells. Isolation of Hoechst 33342 dye extruding cells from SCC of Head and Neck has revealed that these cells demonstrate the ability to self-renew in-vivo with ad-

ditional tumorigenic and chemoresistant abilities. Hoechst 33342 dye can be considered as a tumor marker for tumor-initiating cells of SCC of Head and Neck while the cells demonstrating efflux of Hoechst 33342 dye can be identified as tumor-initiating cells (50).

### GRP78

Imperatively, knockdown of GRP78 diminishes self-renewal and tumorigenicity in nude mice recommending that GRP78 is not simply a marker for tumor-initiating cells but also connected to their ability to self-renew and differentiate into different tumor cell types. GRP78 is an endoplasmic reticulum chaperone protein that additionally manifests itself on the cell membrane and is fundamental for the survival of embryonic undifferentiated cells, apparently by acting in the endoplasmic stress reaction pathway. As of late, glucose regulated protein 78 (GRP78) was utilized to recognize tumor-initiating cells from the SCC of Head and Neck cell line. GRP78 is required for tumorigenicity, invasion, and metastasis of SCC of Head and Neck. GRP78 is overexpressed in a few growths including SCC of Head and Neck, and co-expression of the undifferentiated cell marker Nanog with GRP78 is connected with the diminished survival of SCC of Head and Neck patients (51, 52).

### c-Met

c-Met was as of late explored as a marker for tumor-initiating cells from the SCC of Head and Neck. It is a tyrosine kinase receptor for hepatocyte growth factor (HGF), is related to metastasis, tumor invasion, and diminished survival. The tumorigenic capability of c-Met<sup>+</sup> cells at the point, when contrasted with CD44<sup>+</sup> cells, was observed to be higher. Additionally, the joined tumorigenic capability of c-Met<sup>+</sup>/CD44<sup>+</sup> was observed to be higher when contrasted with individual tumor-initiating cell marker. Conventional chemotherapy resistance present in few malignant tumors has been connected with the stimulated c-Met expression clinically. Henceforth, c-Met expression cannot just be considered as a marker for tumor-initiating cells but additionally as a clinically pertinent remedial focus for a few patients with acquired resistance to chemotherapy. Additional research with a more prominent number of tests to decide tumorigenic capability of c-Met consolidated with different markers like CD44 and ALDH1 is yet to be accomplished (53-55).

### Squamospheres

A squamosphere is a solid, spherical formation developed from the proliferation of one progenitor cell. Cells

are grown in the serum-free, non-adherent conditions in order to enrich the progenitor cell population as only progenitor cells can survive and proliferate in this environment. In SCC of Head and Neck, these squamospheres have been shown to be enhanced for stem cell markers, including CK5, OCT4, SOX2, and nestin (56-59).

### Treatment modalities targeting tumor-initiating cells of SCC of head and neck

The current treatment modalities for SCC of Head and Neck are centered on aimless cytoreduction by use of chemotherapy and radiotherapy. Considering the current scenario, tumor-initiating cells provide vital ramifications in regards to the malignancy treatment. The tumor-initiating cell theory proposes that exclusive targeting of tumor-initiating cells will cause the successful elimination of the tumor. In spite of this, there is a considerable proof that tumor-initiating cells have characteristic medication and radiation resistance causing tumor recurrence regardless of the huge decrease in the tumor size. The component behind resistance varies. Radiation resistance is owing to increased DNA repair, while imperviousness to chemotherapy is often times related to drug transport and metabolism, rendering most customary treatments inadequate.

A considerable amount of work is being done to comprehend the molecular mechanisms selective to the pathobiology of tumor-initiating cell, which will permit unique and focused treatment. Considering the role of tumor-initiating cells in tumor progression and metastasis, the treatment modalities for SCC of head and neck might be focused on the inhibition of tumor-initiating cells, promoting the angiogenic inhibitory factors, and enlistment of the tumor-initiating cells towards differentiation and maturation.

Numerous pharmaceutical organizations have formulated medications to focus on the pathways in tumor-initiating cell formation. The capacity of these medications to specifically target tumor-initiating cells while saving normal tissue stays faulty and is basic for the future use of stem cells in cancer treatment. Particular attention on the reactive oxygen species status of tumor-initiating cells is likewise recommended to demonstrate compelling in treatment by modification of intracellular milieu which will encourage programmed cell death over the proliferative effects. Nonetheless, targeting the different transduction pathways required in tumor-initiating cell development like Indent, Wnt, and Hedgehog has given promising outcomes in targeted cancer treatment (60-63). Studies to make tumor-initiating cells chemo-radiosensitive

have been endeavored in SCC of Head and Neck by means of knockdown of Bmi-1 and CD44. Due consideration should be given to the specificity of drugs used. The drugs that target tumor-initiating cells must stay away from harming normal non-cancerous cells, to be clinically helpful (48, 64). The association of tumor-initiating cells with angiogenesis has already been demonstrated. The local microenvironment gives the ability of self-renewal and maintenance, animating fundamental signaling pathways in tumor-initiating cells and prompting to the discharge of elements that advance angiogenesis and development of tumor-initiating cells (65). Henceforth, the part of targeting on angiogenesis in the treatment of carcinomas cannot be disregarded. This is a critical calculated methodology for focused disposal of malignant undifferentiated cells through the interruption of their supportive local microenvironment (66). The consequences of antiangiogenic treatment are entrancing; however, it must be considered with an alert. It has been conceptualized that the malignant cells may procure an invasive phenotype trying to escape from the ominous tumor microenvironment created by the impacts of antiangiogenic medications by means of mechanistic pathways of resistance (48, 67). Comparative research in light of differentiating the tumor-initiating cells in SCC of Head and Neck into mature, non-malignant epithelial cells can be attempted by use of their ability of differentiation. Tumor-initiating cell, a type of undifferentiated cell, possesses an inborn veiled limit of differentiation. This process of differentiation is directed by different differentiation elements like bone morphogenetic proteins, which under ordinary conditions incite differentiation of neuron precursors into mature astrocytes (68). In light of the recent updates on the treatment of tumor growth, we propose a multistrategy approach which may demonstrate success instead of customary treatment which has been unsuccessful to improve the morbidity and mortality of head and neck cancer patients. Focusing on tumor-initiating cells shapes the backbone of the proposed multistrategy approach which joins routine treatment which conceivably takes into account cytoreduction and tumor cell initiating therapy which may avert recurrence and metastasis.

## Conclusion

Contemporary advances in sub-atomic procedures have helped in better understanding the part of tumor-initiating cells in cancer progression. Endeavors and further research are still supported to decide particular markers and strategies to explicitly target these cells. With the disturb-

ing ascent in a number of new malignancies detected worldwide and reasonable achievement rates of current remedial procedures, another approach in combating tumors which will help diminishing mortality and also bleakness of patient should be critically addressed. We are carefully hopeful about the achievement of tumor-initiating cell targeted therapy which will address the inadequacies of ordinary treatment and will advance as a center methodology in eventual fate of treatment of carcinomas. Research relating to SCC of the Head and Neck stay constrained and a large portion of the speculations depend on cancers from different organs/tissues. More research identifying tumor-initiating cells of SCC of Head and Neck ought to be attempt which will help in the treatment of the malignant disease.

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## Potential conflict of interest

Authors declare no conflict of interest related to the article.

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