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Cancer stem cells in head and neck squamous cell carcinoma

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Abstract

Cancer stem cells (CSCs) are cancer cells that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. CSCs are therefore tumorigenic. The existence of CSCs is under debate and the origin of CSCs is an active research area. CSCs may generate tumors through the stem cell processes of self-renewal and differentiation into multiple cell types. Cancer stem cells (CSCs) have been identified in head and neck squamous cell carcinoma (HNSCC). So, development of specific therapies targeted at CSCs holds hope for improvement of survival and quality of life of cancer patients, especially for patients with metastatic disease like (HNSCC).

Keywords: Squamous cell carcinoma, cancer stem cells, head and neck

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the world's top ten most common cancers. Current survival rates are poor with only 50% of patients expected to survive five years after diagnosis. The poor survival rate of HNSCC is partly attributable to the tendency for diagnosis at the late stage of the disease [1]. HNSCCs are rather challenging to manage because of their heterogeneity in the natural history and the demand for not only better tumor control but also improved functional and cosmetic results [2]. One of the reasons for treatment failure is thought to be related to the presence of a subpopulation of cells within the tumor called cancer stem cells (CSCs). Epithelial tumors, including head and neck squamous cell carcinoma (HNSCC), contain cellular heterogeneity, some of which is accounted for by ongoing mutations that occur because of genetic instability and environmental factors [3, 4]. CSCs are highly tumorigenic compared to the other cancer cells and are believed to be largely responsible for the biological characteristics of cancer, namely, rapid growth, invasion, and metastasis [5]. CSCs also show a greater capacity for migration, invasion, and proliferation in vitro [6, 7].

The purpose of this article is to review many of opinions and discussions about the existence of cancer stem cells, its origin, and role in (HNSCC) in addition to identification, markers, metastasis and treatment.

2. Normal stem cells

Stem cells can be divided into three categories: embryonic, germinal, and progenitor somatic stem cells. Embryonic stem (ES) cells are derived from the inner cell mass of the blastocyst. ES cells are omnipotent and are precursors of all cells of the organism. ES cells differentiate to all cell lineages in vivo and can differentiate into many cell types in vitro. Embryonic stem cells give rise to cells that form various organs by the process of determination [8].

Compared with ES cells, tissue-specific adult stem cells reside in adult tissues, they have less capacity for self-renewal and, although they differentiate into multiple lineages, they are not omnipotent. Progenitor somatic stem cells in adult organisms are responsible for normal tissue renewal and potentially for repair of small damages of tissues. The appropriate differentiation into tissue specialized cells is induced by factors of the local milieu in the body, by cell fusion, and some other so far unknown molecular mechanisms. Germinal stem cells in the adult are responsible for production of eggs and sperm [9].

A major characteristic of stem cells is their ability for self-renewal without loss of proliferation capacity with each cell division. In addition stem cells have the capacity to divide for long periods of time in an environment where most of the cells are quiescent. Recently it was reported that micro RNAs expression is required for stem cells to bypass the normal G1/S checkpoint [10]. While the ability of adult human stem cells exist throughout the life of the organism is attributed to telomerase activity. In comparison to embryonic stem cells, the ability of some adult stem cells to maintain their telomeres seems to be limited and is not sufficient to prevent their senescence. Consequently adult stem cells are at higher risk of malignant transformation [11].

3. The origin of CSC

The origin of CSCs is an active research area. The answer may depend on the tumor type and phenotype. So far the hypothesis that tumors originate from a single "cell of origin" has not been demonstrated using the cancer stem cell model. This is because cancer stem cells are not present in end-stage tumors. Origin hypotheses include mutants in developing stem or progenitor cells, mutants in adult stem cells or adult progenitor cells and mutant, differentiated cells that acquire stem-like attributes. These theories often focus on a tumor's "cell of origin".

Recently, efforts have been made in isolating CSCs from human cancer samples as well as animal models as summarized in. Although most of these studies are able to show cancers initiated by certain enriched populations for CSCs, homogeneity has not been reached. In fact, data revealing that CSCs can originate from either stem cells or progenitors raise the possibility that multiple CSC populations may be formed during cancer progression and even co-exist in advanced cancers [12, 13].

The stem cell population is a logical candidate as a target for oncogenic transformation because of the inherent abilities of self-renewal and multiline age differentiation [14].

In addition to stem cell origin, recent findings point out that CSC can also arise from committed progenitors that acquire self-renewal capacity. Such progenitors are normally derived from self-renewable HSC but have no or very limited self-renewal capacity. With progressive proliferation and differentiation, these progenitor cells are capable of producing terminally differentiated functional cells [15].

Although CSCs are generally considered to be derived from mutated stem cells or progenitors of corresponding tissues or organs, some surprisingly originate from cells recruited from other tissues [16].

4. Cancer Stem Cells in Head and Neck Squamous Cell Carcinoma

The first report with evidence of CSCs in HNC was identified a CD44+ population from primary human head and neck cancers that was tumorigenic in nude mice [17]. CD44 is a transmembrane glycoprotein, with several isoforms that differ in their extracellular domains, and serve as a receptor for hyaluronic and there are several contradictory reports on the utility of CD44 as a marker for HN-TIC [18].

Researches highlight the need for more specific markers or combinations of markers and activity assays for identifying HNCSCs like aldehyde dehydrogenase ALDH. The combined use of the ALDH and CD44 have enabled isolation of HNCSC from primary human tumors [19].

Recently, glucose regulated protein 78 (GRP78) was used to identify HN-TIC from the HNSCC cell line, SAS [20]. GRP78

is an endoplasmic reticulum chaperone protein that is required for tumorigenicity, invasion, and metastasis of HNSCC. A number of studies have suggested that CD133+ cells isolated from head and neck squamous cell carcinoma cell lines display increased clonogenicity, an EMT phenotype, tumor sphere formation, self-renewal, proliferation, multilinear differentiation, and tumorigenicity [21-23].

Also c-Met, a tyrosine kinase receptor for hepatocyte growth factor (HGF), is associated with metastasis and tumor invasion, decreased survival, and was recently investigated as a marker for CSCs in HNSCC [24-26].

5. The effect of CSC on HNSCC treatment therapies

At the beginning chemotherapy and radiation were an essential treatment for HNSCC whereas the CSC hypothesis suggests that the elimination of CSCs is the only way to treat cancer effectively. So we will face a serious problem because CSCs have inherent drug and radiation resistance. Radio resistance of CSCs has been attributed to their self-renewal capacity, DNA repair capacity, free-radical scavenging, upregulation of cell cycle control mechanisms and specific interactions with the stromal microenvironment. Chemotherapy resistance is frequently related to accelerated drug transport and to drug metabolism [27].

Many studies show that Bmi-1 and CD44 knockdowns have led to an improvement of CSCs chemosensitivity in HNSCC. Knockdown of CD44 increased the sensitivity of HNSCC cells to cisplatin, underlying the crucial of CSCs in the response to chemotherapy [30] whereas Bmi-1, a stem-cell-related gene, which participates in the self-renewal of hematopoietic and neuronal stem cells, and has been implicated in the tumorigenesis of various malignancies the experiment showed that that knockdown of Bmi-1 increased the effectiveness of radiotherapy and resulted in inhibition of tumor growth in nude mice transplanted with ALDH1+ CSCs [28].

Bertrand *et al.* [29] demonstrated that the combination of UCN-01 (a checkpoint kinase inhibitor) and ATRA (all-trans retinoic acid) with irradiation decreased the survival fraction of CSCs and could be used as a powerful radio sensitizing strategy in HNSCC.

Other researches depend on the immune response to develop antitumor T-cell vaccines antigen ALDH1A1+ of CSCs. The study proves the ability in vivo of generated ALDH1A1-specific cytotoxic T lymphocytes to eliminate ALDH (bright) cells present in HLA-A2+ HNSCC carcinoma cell lines. They also found antitumor activity by adoptive immunotherapy with ALDH1A1-specific cytotoxic T lymphocytes in vivo. The elimination of ALDH (bright) cells thanks to ALDH1A1-specific CD8+ T cells could inhibit tumor growth and metastases [30].

6. Conclusion

The understanding of CSC roles and their effects on cancer is a very sophisticated thing but very important for trying to find new therapies which could save life of millions patients. Now the advances in nanotechnology could represents a novel area for future research in HNSCC.

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