ejpmr, 2016,3(3), 162-166

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

ROLE OF STEM CELL IN DIAGNOSIS AND TREATMENT OF ORAL CANCER

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Article Received on 29/12/2015 **Article Revised on 19/01/2016** **Article Accepted on 10/02/2016**

ABSTRACT

Oral squamous cell carcinoma is one of the world most common cancers with its highest occurrence in the Indian subcontinent and different aggressive and etiological behavioural patterns. The scenario is only getting worst by the day with the drop in 5 year survival to 50%, persistent treatment failures and frequent cases of recurrence. One of the major reasons for these failures is the presence of cancer stem cells (CS that are highly tumorigenic small group of cancer cells, with self-renewal properties and have the ability to differentiate into cells that constitute the bulk of tumours**.** Cancer-initiating cells show aberrant phenotypic and functional characteristic features. These are similar to normal stem cells from which they are evolved by accumulation of multiple cytogenetic and/or epigenetic alterations. Signal transduction pathways which are essential for normal stem cell function are abnormally expressed by cancer cells. A cancer cell phenotype plays an essential role in cancerization and metastasis.

KEYWORDS: Oral squamous, cancers, cancerization and metastasis

INTRODUCTION

Squamous Cell Carcinoma of head and neck (SCCHN) is the most common malignant condition in the world. Its ranked 8th and 13th for males and females respectively. OSCC has a high occurrence in India due to the increased incidence of lifestyle habits like betel quid and areca-nut, chewing tobacco which enhance the risk.[1]

Despite the recent advances in first line treatments, the 5 year survival rate after treatment remains disappointingly low at about 15-50% for the past 3 decades.[2,3] This will lead to poor prognosis, which because of low response rate to current therapeutic strategies, late stage diagnosis, high risk of recurrence and aggressive metastases. This is strongly suggestive of an urge to improve the diagnostic capabilities and treatment efficacy. Research in cancer therapeutics has helped in targeting those pathways that appear to contribute in tumorigenesis and metastasis with greater efficacy and fewer unwanted side effects. The different organs in humans are constituted by tissues with mature and specialised cells and its specific stem cells. Only a small fraction of cells are represented by stem cells that constitute each tissue. These are the only cells having self-renewal capacity.

The similarities between cancer cells and stem cells was seen long back. In animal model, the ability of the a small population of cells to originate a new malignant neoplasia was demonstrated in a classic experiment utilising transplantation of cells from acute myeloid leukaemia that expressed certain cell surface markers associated with normal haemopoitic stem cells (Lapidot et al.,1994.[5]

Increasing experimental evidence supports the cancer stem cell model, which suggest that these small proportion of cells have the capability of sustaining tumour formation, tumour growth, self-renewal &differentiation. In the late 1970s cancer stem cell (CSC) theory of tumorogenesis was originally proposed. This was first explained in hematologic malignancies in 1994.[5] Since that time, CSCs have been identified in multiple other lung, colon, pancreatic cancer, solid organ malignancies, including central nervous System (CNS), and very recently in oral squamous cell carcinoma. These CSCs also suggests probable role of these CSC in resistance to therapy. CSC played an important role in establishing the metastasis and recurrence. This in turn is allusive of the fact that targeted removal of these CSCs could become a new trend in the treatment of oral cancer (Prince et al., 2007; Satpute et al., 2013).[6]

Relation of Cancer Stem Cells (CSCs) to Tumorigenesis: A tumor appears as an "organ" composed of transformed cells that interact with stromal cells within the tumor microenvironment.[7] This process of tumorigenesis requires multistep initiation of cellular and molecular pathways leading which leads to a series of mutations resulting in replication and growth factor independence, resistance to growth-inhibitory signals, tissue invasion, andmetastasis.[8]

Related theories suggest that there are currently two accepted models for cancer development as follows:[9]

i) The stochasticmodel suggests that every cancer cell has the ability to initiate a new tumor growth equally.
ii) The alternate hypothesis indicates that every tumor has a rare group of cellscalled cancer initiating cells (CICs) or cancer stem cells.[8]
iii) The most recent key features of the cancer stem cell hypothesis were described by **Prince and Ailles in 2008** which stated that (1) only a small fraction of the cancer cellswithin a tumor have tumorigenic potential when transplanted into immunodeficient mice (2) the cancer stem cell subpopulation can be separated from the other cancer cells by distinctive surface markers (3) tumors resulting from the cancer stem cells contain the mixed tumorigenic and non-tumorigenic cells of the original tumor (4) the cancer stem cell subpopulation can be serially transplanted through multiple generations, indicating that it is a self-renewing population.[10]

Stem cells: The concept of CSCs first began 150 years ago when Rudolph Virchow, A German pathologist, found similarities between embryonic and tumor tissues. CSCs were first experimentally defined in hematopoietic malignancies by Lapidot and colleagues in 1994.[11] Al-Hajj et al., in 2003, using breast tumors cells concluded that CSCs were heterogeneous in nature. Primary breast cancers contained few cells which had the capacity of initiating tumors, while tens of thousands of phenotypically different cells did not.[12] Gao in 2009 identified precancerous stem cells (pCSCs) in cancer and suggested that both CSC and pCSC may act as precursors of tumor stromal components for e.g. tumor vasculogenic stem/progenitor cells (TVPCs). Hence Gao recommended, how tumor-initiating cells developed.[6] Tumor-initiating cells (TIC) is initiated from precancerous stem cells (pCSC)leading to CSC and later cancer, a cellular process that parallels the histological process of hyperplasia/metaplasia (TIC) from precancerous lesions(pCSC) into malignant lesions. Stem cells, after fertilization of egg cell results in creation of totipotent cells, which are precursors of all tissues of embryo. After 4 days of fertilization these totipotent cells undergo several mitotic divisions to form identical cells and after this point, they tends to lose their high proliferative potential and become specialized cells and known as pluripotent cells. These cells further divide and become mature and form more specialized multipotent cells and are committed to form specific cell groups that have distinct functions. Further- more multipotent cells divide and give rise to unipotent stem cell which are able to differentiate into only one cell lineage. Finally these cells converted to nullipotent cells that terminally differentiated and have lost their self-renewal capabilities. Nowadays, cancer is increasingly being viewed as a stem cell disease, both in its propagation by a minority of cells with stem-cell-like properties and in its possible derivation from normal tissue stem cells. The stem cell actions are tightly controlled, which raises the issue of how normal regulation might be subverted in carcinogenesis.[13]

Cancer Stem Cells: The cancer stem cells or "tumor-initiating cells "or tumor progenitor cells which are capable of initiating tumor formation. However, the bulk of the tumor is composed of rapidly proliferating cells called transit-amplifying cells and post-mitotic differentiated cells. This subpopulation of 'cancer stem cells' exhibits same nature as of normal stem cells,[14] although they are not necessarily derived from normal tissue stem cells.[15] 'Cancer stem cells' (CSC) has been highly debatable in the literature. Cancer stem cells includes functional characteristics of these cells, and its ability to generate tumors in immunodeficient mice, self-renewal, and multipotency.[18]

Currently, there are two hypothetical explanations for the survival of CSCs that state they may arise from normal stem cells by mutation of genes that make the stem cells cancerous or they may also come from differentiated tumor cells that show prominent genetic alterations and hence, become dedifferentiated and acquire CSC like features.[19] It is well known that cancer stem cells possess innate resistance mechanisms against chemotherapy and radiotherapy, in turn stopping therapy-induced cell death leading to their survival and also promote tumor recurrence. Notably, the demonstration that the most tumorigenic sub-set of cells within a tumor is also uniquely resistant to therapy provides strong basis for studies focused on the understanding of mechanisms reinforcing this resistance.[20]

Understanding what controls the maintenance of stem cells and differentiation signals may give insight into the cellular signals involved in cancer, and may ultimately lead to new approaches to management of cancer.

Cancer stem cells markers

CD44 marker is a transmembrane glycoproteins. It is cell surface receptor for hyaluronic acid and expressed as several isoforms. It is involved in cell adhesions, migration and metastasis.[21] CD44+ subpopulation demonstrated its tumorigenic potential, tumour sphere formation and chemo-resistance in both cell lines and primary tissues of oral squamous cell carcinoma.[22] The positive population of these cells also coexist with certain stemness markers like Bmi1 that maintains the undifferentiated state of the cell (Prince et al., 2007).[23,24]

CD133 marker is a cell surface marker. It is also known as prominin -1. It was discovered as a marker of normal haematopotic stem cells. In OSCC, CD133+ cells displayed increase in clonogenicity.

Primary tumors and oral cancer stem like cells from cell lines were found to have an increased expression of CD133, and displayed increased migration and

tumorigenicity when compared to controls.[26] Furthermore; CD133status has been associated with poor cancer prognosis for HNSCC patients.[27]

Aldehyde dehydrogenase (ALDH) comprises of a family of intracellular cytosolic enzymes that are mostly found in the liver.[28] Their known functions include the conversion of retinol to retinoic acid in early stem cell differentiation. It helps in catalyzing the oxidation of toxic intracellular aldehyde metabolites, similar to those formed during alcohol metabolism and chemotherapeutics, into carboxylic acid (Chen et al., 2009).In OSCC, increased levels of ALDH correlated with disease staging, radio-resistance and negative correlation prognosis (Chen et al., 2009). In several labs, ALDH was found to enrich for cancer stem cells and is involved in epithelial-to-mesenchymal transition. More recent evidence supports the use of ALDH+ as a single marker to identify cancer stem cells in HNSCC.[30]

Growth factor (HGF) also called as tyrosine kinase receptor. Normally only stem cells and progenitor cells express Met, however, CSCs seize this ability which is from the normal stem cells expressing with tumour invasion and metastasis, leading to decreased survival and angiogenesis in various neoplasms.[27] In HNSCC, c-Met+ cells demonstrated self-renewal and were able to generate heterogeneous tumours with more tumorigenic potential than by *CD*44+ marker.[28]

Side population is defined as a sub-group of cells that behave differently than the main population when analyzed with a specific marker. Cell multidrug transporters efflux of vital dyes has been investigated as a potential marker for cancer stem cells. The cells' ability to actively pump the dye Hoechst 33342 by the ATP-binding cassette transporter (ABC) can be used to identify cells with increased longevity, and this concept is applicable to cancer stem cells which remain in a quiescent state.[31] Zhang and colleagues demonstrated that oral squamous cell carcinoma's SP cells exhibit features consistent with those of cancer stem cells.[32]

Stem Cells Niches: It is generally believed that stem cells reside in 'niches' or specialized local microenvironment that are conducive to their function.[33] Niches create a complex environment. Here complex interactions among cells and matrix components define stem cell survival and stemness. Evidence proves a supportive perivascular niche present in head and neck cancer.[34] We observed that the majority of the cancer stem cells are found within a 100 m-radius of blood vessels in primary human HNSCC. These data demonstrated that disruption of the tumor vasculature is sufficient to reduce the ratio of tumor-initiating cells in pre-clinical models of HNSCC thus providing evidence for the presence of a supportive niche for stem cells in these tumors.[33] In head and neck squamous cell carcinomas, the majority of the stem cells are located in close proximity to the blood vessels. They rely on interactions with other components of the niche for their survival (Krishnamurthy *et al*., 2010). In addition to providing oxygen and nourishment to the cells and factors secreted by endothelial cells promote the self-renewal and survival of head and neck cancer stem cells.

Challenges in Head and Neck Cancer

One of the biggest challenges in cancer stem cell research has been the development of methods for culture, expansion, and analyses of undifferentiated cancer cells. Anchorage independence which is ability to survive in suspension has been used for this purpose (Jensen and Parmar, 2006). The method of enriching for cancer stem cells by sphere generation under low attachment culture conditions has been suggested and used in various models of cancers such as neural, breast and prostate (Dontuet al., 2003; Pastranaet al., 2011) and also adapted for HNSCC (Krishnamurthy et al., 2010). The expansion of cancer stem cells is frequently performed in vivo, which is time-consuming and expensive.

However, limited capacity is offered by methods in vitro for cancer stem cells expansion in an undifferentiated state. It has become clear that the development of improved methods for isolation and expansion of head and neck cancer stem cells is essential for the acceleration of the pacy discovery in this area.

CONCLUSION

It is renowned that a frequent cause of failure of conventional therapy in HNSCC is the high incidence of local recurrence and distant metastasis. Remarkably, it has been hypothesized that conventional therapies do not eliminate the slow-growing cancer stem cells, which appear to be the "drivers" of tumor recurrence and metastases. Hence, the current observation that HNSCC might follow the cancer stem cell hypothesis suggests that targeted elimination of these tumor-initiating cells will prevent tumor recurrence and distant diseases. Therefore expansion of cancer-stem-cell-based therapies will have a positive impact on the survival of patients with head and neck cancer in the future.

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