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Role of Stem Cells in Oral Cancer

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ABSTRACT

Cancer stem cells have been discovered in squamous cell carcinoma of the oral cavity. In oral cancer, cancer stem cells play a crucial role in tumour development, as well as increased recurrences, acquired treatment resistance, and metastasis. Cancer stem cells have the ability to self-renew and multiply forever, producing progenitor cells and cancer cells that feed tumor growth. Many cancers, including oral cavity squamous cell carcinoma, have been identified as cancer stem cells using specific markers, albeit it's still unclear where these markers fit into the stem cell hierarchy. In the development of cancer, the tumor microenvironment exerts a great deal of pressure. The significance of stem cells in mouth cancer was examined in this article. This is confounded by the presence of many CSC subtypes within OCSCC, which makes the study more difficult. The current state of knowledge in CSC markers SOX2, NANOG, ALDH1, OCT4, phosphorylated STAT3, CD133, CD24, CD44, and Musashi-1 is examined in this study, with an emphasis on their application and validity in Oral cavity squamous cell carcinoma the cancer stem cells research, as well as how they may be grouped into the CSC hierarchy, based on the deployment of a large number of markers. The renin–angiotensin system is also expressed in oral cavity squamous cell carcinoma cancer stem cells, suggesting that regulating the RAS with existing medications might be a novel therapeutic target for CSCs.

Key words: Stem cells, Oral cavity, Tumor, Cancer, Stem cell marker, Carcinogenesis, Tumorgenicity, Cells, SCC, Carcinoma *in situ*

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INTRODUCTION

According to ladder, the OCSCC has a 50% 5 years survival rate [1,2]. Cancer stem cells are more tumorigenic than other cancer cells, and they are assumed to have stayed relatively unchanged over the last four decades [3]. Oral squamous cell carcinoma accounts for more than 90% of all malignant oral lesions, with around 300000 new cases being diagnosed each year across the world [4]. The anatomic region where cancer of the oral cavity occurs, according to the Global cancer observatory database, includes the palate, oropharynx, nasopharynx, preform sinus tonsils, tongue, and other ill-defined locations of the oral cavity, lips, and pharynx. In the year 2012, there were roughly 300373 new cases of oral cavity cancer and 142,387 new cases of other pharyngeal cancer (excluding nasopharyngeal cancer) all over the world [5]. IN immunocompromised engrafts mice, tumours are much larger and there are substantially less transplanted cells than in unsorted cancer cells. Cancer stem cells are resistant to cisplatin, carboplatin, doxetaxel, paclitaxel, topside, gemcitabine, and 5-fluorouracil of RT and CT medicines in oral cavity squamous cell carcinoma [6]. The fast collection of evidence revealing the presence and relevance of CSCs in carcinogenesis has been aided by the introduction of accurate markers and advances in cell biology. Cancer stem cells are clearly distinguishable [7]. This article investigates the most often used markers in cancer stem cell research into oral cavity squamous cell carcinoma and attempts to place them in the context of a hierarchical cancer model.

LITERATURE REVIEW

Master regulators of embryonic stem cell marker

NANOG and OCT4 are two of the six key components involved in transforming somatic cells into ESC-like states. The master regulators for stem cell renewal and maintenance in the undifferentiated state are assumed to be OCT4, SOX2, and NANOG. NANOG is significantly expressed in both peritumoral tissue and tumour as compared to normal tissue.

Carcinogenesis is caused by abnormal cell reprogramming. The factor of transcription for OCT4 is a POU domain

regulator that is important for early embryogenesis and ESC pluripotency maintenance within oral cavity squamous cell carcinoma, OCT4 is thought to have role in tumourtumerogenicity, invasion, metastasis, transformation. It is also suggested that OCT4 contributes to the initation of tumour by the epithelial–mesenchyme transition regulation. OCT4 is involved in aberrant cell reprogramming, which results in carcinogenesis. In moderately differentiated buckle mucosa, OCT4 has been detected in a distinct subpopulation of cancer stem cells inside tumour nests, the peritumoral stroma, and the micro capillaries in the peritumoral stroma. In moderately developed oral tongue squamous cell carcinoma, OCT4 expression is restricted to a subpopulation of CSCs inside the peritumoral stroma.

SOX2: The SOX2 protein is an SRY-related high mobility group box transcription factor with a high mobility [8,9]. SOX2 is engaged in a variety pathway of signal transduction and it is linked to cell invasion, migration, carcinogenesis, stamens chemo resistance, anti-apoptosis and proliferation, in both pathological and normal processes .It is shown to interact with OCT4 in OCSCC mouse cell [10]. It's been demonstrated that it regulates the downstream embryonic genes such as NANOG. SOX2 overexpression has been used in concert with other markers to detect cancer stem cells in squamous cell carcinoma, specifically oral cavity squamous cell carcinoma, such as ALDH1, NANOG, and OCT4 CD44. In BMSCC, SOX2 is found in tumour nests, peritumoral stroma, and micro vessel endothelium within the peritumoral stroma. In OTSCC, cells that express SOX2 also express SALL4, phosphorylated STAT3, CD44, and NANOG. In oral cavity squamous cell carcinoma, SOX2 expression is much lower in normal tissue than in tumour tissue, and it is only modestly connected to OCT4. The Lin 28B-Let 7 pathway governs SOX2 and OCT4 expression in oral cavity squamous cell carcinoma specimens, and the Lin 28B high-Let 7 low expression pattern is significantly associated to a high proportion of CD44+/ALDH1+ CSC in oral cavity squamous cell carcinoma [11].

Signal transducer and activator of transcription Long recognised as an oncogene involved in anti-apoptosis and cell cycle progression, STAT3 and signal transducer is now being studied further.

NANOG: Compared to the paternal population, the CSC population is overexpressed. Linked to transformation of tumour. Tumorigenicity and metastasis are two terms used to describe the ability of a substance to cause tumour and spread [12]. NANOG has been found to be increased in a variety of malignancies and to have a part in oral cavity squamous cell carcinoma, tumour tumogenesis, metastasis and transformation. NANOG overexpression has also been linked to poor chemo resistance and differentiation [13]. Enlarged NANOG expression has link to a poor outcome in OCSCC patients.

Cancer stems markers of OCSCC

CD44: CD44 expression in CSCs is substantially higher in oral cavity squamous cell carcinoma, cell lines than in parental cells [14]. In epithelial malignancies, particularly OCSCC, it has been frequently employed as a CSC marker. CD44 found in oral epithelium which is normal, cancer in situ, and certain lymphocytic infiltration, with carcinoma cells having the greatest expression [15,16]. CD44 expression in cancer stem cells is higher in OCSCC cell lines than in parental cells. In epithelial malignancies, such as oral cavity squamous cell carcinoma, it has been frequently employed as a cancer stem cell marker. CD44 is expressed by normal oral epithelium, cancer in situ, and some lymphocytic infiltration, with carcinoma cells expressing the highest. In numerous solid tumours, including oral cavity squamous cell carcinoma, expression of the variant isoform CD44 v6 has been linked to depth of invasion, perineural invasion, regional nodal metastasis, pattern of invasion, and local recurrence. It was observed that CD44 cleavage regulated by ADAM17 is needed for tumour sphere formation in oral cavity squamous cell carcinoma. Growth of CD44 expression shows a restricted connection with high histological class and late clinical stage, on the other hand, found no link between poor prognosis and CD44 expression and in OSCC.

CD24: It is tiny surface glycoprotein that is been found in a broad range of cancer cells which is implicated in metastasis and cell adhesion [17]. CD24+ cells have antigenic potential, according to a current study utilising grade OSCC cell in a NOD/SCID mouse version. CD31 expression revealed that tumours produced from CD24+ cells had a much higher functional capillary density than those implanted with CD24 cells [18].

CD133: CD133 is a pent span Tran's membrane protein that aids in the organisation of plasma membrane structure. CD133 was initially discovered overexpressed in hematopoietic stem cells and endothelial progenitor cells, but it is now widely employed as a cancer stem cell marker in a variety of solid tumours, including oral cavity squamous cell carcinoma. CD133+ oral leukoplakia is three times more likely than CD133 lesions to develop squamous cell carcinoma of the oral cavity. Of all the cancer stem cell phenotypes studied, oral cavity squamous cell carcinoma lesions with triple-positive expression of NANOG, CD133, and OCT4 have the lowest survival rate. CD133+ cells also express CD44, and the immunophenotyping CD133+/CD44+ has been linked to a lower overall survival rate, suggesting that cells expressing these proteins are more aggressive. From normal epithelium through dysplasia to cancer, CD133 expression grows in the oral epithelium.

Musashi-1: Within OSCC, Musashi-1 has been identified as a translational regulator. Musashi-1 expression has link to a greater stage of OCSCC and a poor differentiation state, and it is coupled with CD133, this suggests that these two proteins have a role in oral carcinogenesis [19].

ALDH1: Aldehyde dehydrogenase is a cytosolic enzyme that catalyses the conversion of aldehydes to carboxylic

acids using pyridine nucleotides. ALDH is being employed more and more as a cancer stem cell marker in oral cavity squamous cell carcinoma, with ALDH+ cells displaying plasticity by forming tumour spheres in serum-free conditions and the capacity to create ALDH cells *in vitro* [21]. Given that ALDH1+ leukoplakia is more than three times more likely to develop oral cavity squamous cell carcinoma 22, ALDH1 is predicted to have a role in the malignant transition of oral leukoplakia to oral cavity squamous cell carcinoma. Overexpression of ALDH1 has also been linked to nodal metastasis. Snail silencing lowered tumorigenicity by reducing ALDH1 expression and inhibiting cancer stem cell features [23].

Oral cavity squamous cell carcinoma cancer stem cells have been discovered to exhibit RAS components. Within oral cavity squamous cell carcinoma, two cancer stem cell subpopulations express (pro) renin receptor, angiotensin II receptor 1, and angiotensin II receptor 2: one within the tumour nests that express SALL4 and another within the peritumoral stroma that express OCT_4 [24].

Body: CSCs form as a result of epigenetic or genetic changes in resident tissue stem cells, according to one of the most widely accepted theories. As indicated by increasingly sophisticated research, the cancer stem cell hypothesis is changing. Instead of a single small population of cancer stem cells and a large majority of bulk tumors cells, cancer stem cells are divided into a complex hierarchy of diverse, genetically heterogeneous subpopulations. Cancer stem cells are also adaptable, and the complexity of these subpopulations grows as tumors advance. Increased cancer stem cell density has also been linked to a poor prognosis, as measured by high levels of expression of various primitive cell and CSC markers, prompting a rush of research on CSC-related prognostic indicators. Both moderately and poorly differentiated OSCC cells displayed greater levels of OCT4, SOX2, and NANOG in hypoxic conditions, suggesting that CSCs and induced pluripotent stem cells are identical. The tumor microenvironment is increasingly recognized as playing a critical role in tumors genesis, metastasis, and heterogeneity. CSCs in SCC appear to switch between two phenotypes: migratory and proliferative. The development of cancer therapies is clearly hampered by this adaptability. SC research has a lot of potential uses, and directly targeting CSCs is becoming more interesting since it has the potential to be more successful than traditional treatments while also preserving organs and decreasing off-target damage in the short and long term. Squamous cell carcinoma tumour spheres in the oral cavity had greater levels of CSC and metastasis markers, are more invasive, and are cisplatin-resistant. Invasion and metastasis are linked to increased fucosylation activity, as measured by overexpression of fucosyl transferases, and increased production of fucosylated polysaccharides such as Sialyl Lewis X. It's still impossible to find a single "silver bullet" that targets CSCs and effectively eradicates cancer; however, a future cancer therapeutic approach might incorporate a mix of current drugs that target important stages of the RAS to regulate cancer stem cells.

DISCUSSION

CSCs form as a result of epigenetic or genetic changes in resident tissue stem cells, according to one of the most widely accepted theories [25-27]. As indicated by increasingly sophisticated research, the cancer stem cell hypothesis is changing. Instead of a single small population of cancer stem cells and a large majority of bulk tumour cells, cancer stem cells are divided into a complex hierarchy of diverse, genetically heterogeneous subpopulations. Cancer stem cells are also adaptable, and the complexity of these subpopulations grows as tumours advance. Increased cancer stem cell density has also been linked to a poor prognosis, as measured by high levels of expression of various primitive cell and CSC markers, prompting a rush of research on CSC-related prognostic indicators. Both moderately and poorly differentiated OSCC cells displayed greater levels of OCT4, SOX2, and NANOG in hypoxic conditions, suggesting that CSCs and induced pluripotent stem cells are identical. The tumour microenvironment is increasingly recognised as playing a critical role in tumour genesis, metastasis, and heterogeneity. CSCs in SCC appear to switch between two phenotypes: migratory and proliferative. The development of cancer therapies is clearly hampered by this adaptability [28-30].

CONCLUSION

The formation of intratumoral heterogeneity to regulate tumour growth in oral cancer is aided by the molecular interaction between cancer stem cells and the tumour microenvironment. TME houses cancer cells, including cancer stem cells, and provides an immunosuppressive milieu that protects CSCs from genetic and epigenetic misbehaviour. By housing cancer cells, including cancer stem cells, in an immunosuppressive environment, TME shields CSCs from genetic and epigenetic misbehaviour. By housing cancer cells, including CSCs, in an immunosuppressive environment, TME shields CSCs from genetic and epigenetic misbehaviour. CSCs induce considerable ECM remodelling by speeding matrix protein breakdown *via* different proteinases, which aids invasion and metastasis. It's also unclear what molecular route is involved in forming a bond between CSCs and epidermal keratinocytes when oral cancer tumours advance. To summarise, a better knowledge of CSCs and their tumour microenvironment, as well as the discovery of key molecular pathways, should help with CSC therapy.

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