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Cancer Stem Cells: A Roofed Peril in Cancer Therapy

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Abstract

Cancer is considered to be the second primary cause of death worldwide. WHO Global Cancer Observatory (GLOBOCAN) data published in 2018, avowed that cancer is responsible for 9.6 million estimated deaths worldwide. Oral cancer is the sixth most common cancer worldwide; constituting approximately 4% of all cancers and third most common malignancies in India. Squamous cell carcinoma (OSCC) is the most common malignancy to affect the human oral cavity[1-3]. The prognosis of Oral Squamous Cell Carcinoma is poor due to its diagnosis at the advanced stages. Regardless of the recent advancement in the treatment of Oral Squamous Cell Carcinoma, the mortality rate remains high. Hence there is an urgent need for further improvement in cancer therapy and diagnosis to improve cancer survival rates, which is also one of the key goals of the World Cancer Declaration issued by Union of International Cancer Control.

Keywords: Cancer stem cells, Oral Squamous cell carcinoma, Self renewal, Multi Drug Resistance, Epigenetic

Introduction

The global load of cancer persist to increase over centuries as childhood mortality and death from infectious disease decline.[1]During 2007,it was anticipated that there will be more than 12 million new cancer cases worldwide. The risk of being diagnosed with cancer increase with age. Longer the life expectancy, the more likely for a specific mutation to occur in their genome, leading to genetic alterations that may lead to malignant phenotype.

Annual estimated incidence of oral cancer is 2,75,000 and of these 2/3rds occurs in the developing countries[4,5]. There is a wide geographical variation in the incidence of oral cancer and it was found to be high in South East Asia, and parts of Western and Eastern Europe.[3] India has the highest incidence with Sri Lanka and Pakistan ranking top in recent reports[6]. Oral cancer is a major problem in the Indian subcontinent where it ranks among the top three cancer type in the country and is considered as an epidemic in recent centuaries.[4-7]Age-adjusted rates of oral cancer in India is high and accounts about over 30% of all cancers in the country.

The failure in improving cancer survival rates suggested that there are more 'upstream' therapeutic targets during the carcinogenesis process[9]. Cancer stem cells (CSCs) play important roles in tumor formation, metastasis and cancer relapse. This led to the cancer stem cell (CSC) hypothesis, which predicted that cancer arises in genetically aberrant cells with tumor-initiating properties and stem-like character resembling to normal stem cells.

Tumor progression was explained by two models: (1) the clonal (stochastic) evolution model (2) cancer stem cell model.

The **clonal evolution model** upholds that all distorted cells within a tumor mass have carcinogenic potential, with unlimited propagation capacity, and the ailment curing requires the elimination of all tumor cells [9]. This hypothesis is supported by several studies demonstrating that a large number of cancer cells sustain tumor growth when are transplanted into histo compatible mice[10].

The **cancer evolution model** sustain that tumors evolve from a tiny subpopulation of cells called as CSCs or cancer initiating cells, due to their capacity to auto-regenerate, proliferate and induce tumor formation[11]. These properties resist against regular oncological treatments and are likely for incompetence of traditional cancer therapies and lead to tumor recurrence and metastasis[10].

Two hypotheses about CSCs formation include: (1) transformation of normal stem cells or progenitor cells into CSCs, process that occurs through multiple gene mutations as result of genetic and epigenetic instability (2) tumor cells progressively acquire stem cell properties through reversal of ontogeny based on oncogene-induced plasticity[12]. Numerous studies suggest that epithelial-mesenchymal transition (EMT) process characterized by the suppression of epithelial markers (e.g., E-cadherin) and up-regulation of mesenchymal markers (e.g., vimentin, fibronectin and N-cadherin) can also generates cells with stem-like properties[11].

Hallmarks of CSCs

The hallmarks of cancer stem cells are endowed with a number of innate adaptive responses such as quiescence, EMT, increased DNA repair and detoxifying enzymes, metabostemness, immune evasion and over-expression of ABC transporters, which gave them the ability to survive changes in the microenvironment and anti-cancer therapies[13]. Undeniable substantiation recommend that stem-like features may be attained as an outcome of metabolic shifts, which can render normal stem cells or dierentiated cancer cells more vulnerable to epigenetic reprogramming. Thus these cells are more likely to move up the cancer cell hierarchy by their expression of pluripotent genes. The metabolic insults, able to induce this reprogramming into CSCs in the context of a pre-malignant tumor, are collectively termed 'metabostemness'[9-14]

The key characteristics of the CSC subpopulation include: (1) only a small portion of the cancer cells within a tumor have carcinogenic potential when transplanted into immunodeficient mice[15]; (2) the CSC subpopulation can be separated from the other cancer cells by distinct cell surface markers; (3) tumors resulting from the CSCs contain the mixed carcinogenic and non carcinogenic cells of the original tumor; and (4) the CSC subpopulation can be serially transplanted through multiple generations, indicating that it is a self-renewing population[12].

Cancer stem cells own a superior capability to survive current therapeutic regimens thus it cannot successfully eradicate cancer especially when the diagnosis occurs at a later stage. Recent data showed that the CSC subpopulation is enriched after chemotherapy, which suggest that this subset is responsible for the preponderance of treatment failure. Chemo resistance is favored by several mechanisms, among which cellular plasticity is an imperative factor[15].

Nevertheless, the resistance of CSCs to therapy is usually not limited to one drug and this phenomenon referred to as multidrug resistance (MDR). MDR is the result of the endogenous expression of detoxifying enzymes, increased drug Efflux pump levels, enhanced DNA repair activity, reduced drug response and activated survival pathways.[15]

These features, combined with the capability of CSCs to evade the immune system, to activate an epithelial to mesenchymal transition (EMT) program and to adapt their metabolism under scarce nutrient conditions, render CSCs almost an imperishable cancer population.[16,17]

The fail in assessing cancer stem cell response in patients receiving chemo therapy may be a factor adding to tumor recurrence as recommended by many retrospective studies. It is a challenge in current Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for evaluating the efficacy of cancer therapeutics in clinical trials[7,10]. There are many intrinsic drug resistance mechanisms in cancer stem cells which inactivate the action of cytotoxic drugs resulting tumor recurrence. Chemo therapy (CT) drugs influence apoptotic response in differentiated tumor cells, thus confer CSCs with a survival advantage with even greater proliferative potential[8]. The result is that tumor cells repopulate with lineage-dependent genotypic and phenotypic alterations that render CT drugs ineffective and lead to more rapid disease progression and poor prognosis. Conventional therapeutics including chemotherapy and radiation therapy have demonstrated efficacy against many differentiated tumor cell types, but exhibit poor performance against CSC-specific targets, leading to tumor re-growth and metastasis[8].

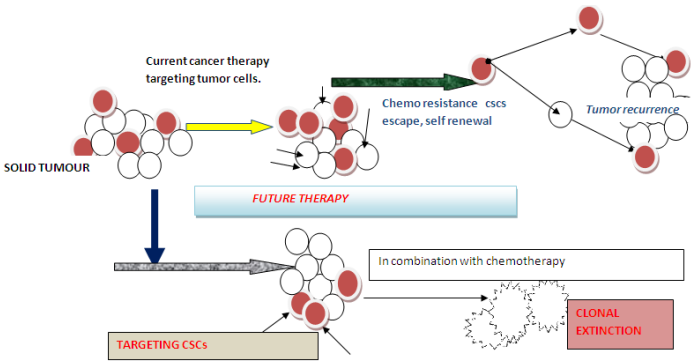

Fig 1: Concept of the cancer stem cell (CSC) .Illustrating the therapaeutic implication on targeting CSCs .

Tumour Cells ◯

Cancer Stem Cells ●

Many schools of thought recently demonstrated that Head and Neck Squamous Cell Cancers contain cancer stem cell, which may self-renew and produce differentiated cells that form the bulk of the tumor. These carcinogenic HNSCC cells have a diverse phenotype and can be identified by a surface marker and reported the isolation of a highly tumorigenic subpopulation of cancer cells from HNSCC. Current treatment for HNSCC regimens may selectively kill the differentiated cancer cells, producing tumor regression while sparing the cancer stem cells, leading to tumor re growth and relapse. Thus literature evidences suggest the role of CSCs in tumor recurrence and chemo resistance in HNSCC .

Conclusion

Millions of people die every year due to oral tumors even after the most sophisticated diagnostic contrivance and management. Tumor recurrence and reversion are obsessed by several molecular events that are amended according to the treatment strain. Recent literature suggests that within the tumor bulk there is a subpopulation of cancer cells, named CSCs, which are mainly responsible for the anti-cancer drug refractoriness. Thus, the frontiers of cancer therapy are aimed at conquering CSCs by using newly revealed drug delivery methods. The successful cancer cures solely depends on prevailing the mechanisms of CSC resistance, which are incongruent and act at divergent levels, including activation of survival pathways, metabolic adaptation, epigenetic modifications and immune escape.. The key mechanisms that regulate CSC function in drug resistance as well as recent therapeutic approaches for targeting CSCs hold promises to new insights of CSCs in drug

resistance which may provide better therapeutic rationales to convoy novel anticancer therapeutics.

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