Origin of Cancer Stem Cells – A Short Review

*** Lavanya A.[1], Shwetha K. N.[2], Vanishri H. C.[3], Roopa S. Rao.[4], Dominic A.[5], and Sowmya S. V.[6]**

*Corresponding Author E-Mail: drlavsmdsop92@gmail.com

Contributors:

[1]Post Graduate Student, [2]Tutor, [3]Assitant Professor, [4]Professor and Head,[5]Assitant Professor, [6]Associate Professor , Department of Oral Pathology, Faculty of Dental Sciences, M.S.Ramaiah University of Applied Sciences, Bangalore-560054

Abstract

Evidences of the current research say that cancer is multi-factorial with varied mechanisms of origin. Globally, it is the second most dominant factor for human death. Most theories disclosed that either intrinsic (genetic) or extrinsic factors were responsible for the cancer development. The cells being triggered by these factors may be somatic (differentiated functional cell) or a normal stem cell with multi-potency or even the transient proliferative cells derived from the stem cells. These stem cells possess several features like slow cell cycle, ability to extrude chemotherapeutic drugs, exhibit epithelial mesenchymal transition and inhibit apoptosis. It is known to play an important role in cancer progression and recurrence. However, the origin of these cancer stem cells still remains debatable.

Keywords: *Cancer Stem Cells, Cell Microenvironment ,Tumorigenic*

1. INTRODUCTION

Human body is exposed to various carcinogenic agents and these agents from the oral cavity reach the respiratory tract and digestive system. Detection and treatment of cancer has dramatically increased due to the rapid development in diagnostics and treatment modalities.[1, 2] Recent evidence has shown that not all cells in the tumour mass show resistance to these treatment modalities. Only a subpopulation of tumour cells possesses certain inherent / acquired properties that enable its survival. These progenitor cancer cells are termed as cancer stem cells (CSCs).[3] This emerging hierarchical thought of tumorigenesis proposes that CSCs sit upon a pyramid of a heterogeneous population of cells within cancer and functionally display stemness characteristics along with asymmetrical division. When comparing to other stem cells, CSCs are highly tumorigenic and considered to be largely responsible for the pathobiology in squamous cell carcinoma (SCC). These CSCs has greater capacity for migration, invasion and proliferation.[1-3] Various studies stated that progenitor cells, differentiated cells and critical gene mutations in stem cells also commit in formation of CSCs. On the other hand, cell microenvironment is critical in CSC self-renewal and differentiation.Hence, this review article discusses about the origin of cancer stems cells (CSCs).

The Origin of Cancer Stem Cells (CSC)

Cancer stem cells are also called as tumor initiating cells (TICs) or cancer propagating cells (CPCs). The CSCs are intraclonally both tumorigenic and non-tumorigenic that carries a capability of proliferation, differentiation and self-renewal. When self-renewing normal stem cells acquire mutations and are transformed by altering proliferative pathways, cancer stem cells may develop (Figure 1). The cancer stem cells also originate by multiple oncogenic mutations in the restricted progenitor cells which possess self-renewal capability. Till date, the origin of CSCs remains unclear. Based on several hypothesis, genetic events such as cell fusion, horizontal gene transfer, inflammatory microenvironment and genomic instability is known to influence the origin of CSCs. Other factors such as stemness, side population and stem cell niche can also have role in CSCs development.[4]

Cell Fusion

Cell-to-cell fusion is a biological process that play important role in formation of bone, muscle tissue and placenta. This biological process has a close relationship with cancer development and progression. It has been shown that several types of cells such as hepatocytes, cardiac myocytes and oligodendrocytes can fuse with hematopoietic stem cells, and contribute to cancer initiation and progression. When the

fusion between a stem cell and a differentiated cell takes place, heterokaryon, a multinucleated cell that contains genetically differentiated nuclei is formed. This heterokaryon acts as an intermediate step and as a by –product synkaryon, a single nucleated cell is formed. The synkaryon is generally characterised by chromosomal loss and leads to CSCs formation, possess both self-renewal activity and transformed ability. Thereby, increased cell to cell fusion closely relate to cancer development.[4]

Horizontal Gene Transfer

Another mechanism involved in origin of CSCs is horizontal gene transfer. It is the transfer of DNA from apoptotic cells to recipient cells by endocytosis or phagocytosis. Mutation of somatic cells due to genetic or oxidative stress may trigger apoptosis. DNA from apoptotic cell is taken up by normal stem /progenitor cells through endocytosis or phagocytosis that results in genetic material reprogramming and CSCs formation. This event often occurs in bacteria and fungi.[4]

Genomic Instability

Genomic alterations and instability are the fundamental basis of tumor development which includes chromosomal gain, loss or derangement. These alterations in gene may occur at chromosome level and represent as aneuploidy. This chromosomal instability results in imbalanced chromosomal number and loss of heterozygosity which enhances the susceptibility of cells to carcinogens. It is accepted that stem cells, progenitor cells and differentiated cells with these alterations can give rise to CSCs and tumor development.[4]

Inflammatory Microenvironment

Inflammatory microenvironment may also act as triggering factor in CSCs formation and clonal selection. Any injury or infection may activate inflammatory response by releasing cytokines and chemokines. The main triggering factor for transformation of normal somatic cells into cancer stem cells was the alteration in the genes responsible for controlling cell proliferation and tumor suppression. Currently researches proposed that during the activation of oncogenes, the main cells involved were stem cells. This mutagenic transformation is chiefly due to the exposure of stem cells to higher concentration of reactive oxygen, nitrogen species (ROS/RNS) and lipid peroxidation products (LPPs) within the presence of chronic inflammation. The most frequently mutated dominant oncogenes in human cancers is RAS gene and they are known to activate the formation of tumor promoting inflammatory mediators such as chemokines and cytokines. These mediators promote the transformation of stem-like cells into immortal cancer stem cells. Epithelial mesenchymal transition (EMT) is immense complex cellular process that is involved in normal embryogenesis, tissue repair, in cancer progression and metastasis. Numerous studies revealed that through the EMT process, normal stem cells can dedifferentiate to cancer stem cells. (Figure 1).[4]

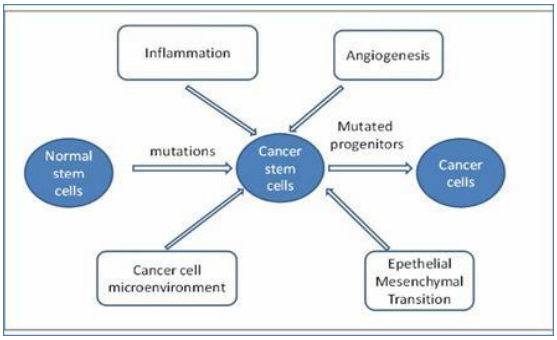

Fig.1 Differentiation of normal stem cells to cancer stem cells

Stemness

As the name indicates CSC possess properties of both stem cell and cancer cell with a property of stemness. Stemness is represented as ability to undergo self-renewal and differentiation. The properties of stemness may be inherited or acquired.[5]

Inherited Stemness

Normal stem cells responsible for physiological

development may develop mutations leading to formation of a multipotent stem cell with tumorigenic properties. Normal stem cells have several properties of survival like, low proliferative index and high self-renewal system enabling a longer life span. These properties allow the physiological stem cells to be the ideal candidate for accumulating mutational alterations finally culminating in the formation of cancer stem cells.

On the other hand, somatic epithelial cells have short life span, and do not exist long enough for mutational accumulation. Further these somatic cells, due to their shorter life span may undergo cell death post mutational damage. Thus, in either scenario, the somatic cells are less likely to be progenitors of cancer stem cells. Cancer stem cell divides in an asymmetric fashion resulting in the formation of a stem cell and a somatic cell. Differentiated (somatic) cell possess low to no stemness, but have transient high proliferative property. Such cells are termed as transit amplifying cells (TAC). These TAC give rise to terminally differentiating cells.[5,6]

Acquired Stemness

Although the somatic or differentiated cell possess little to no stemness, evidence does exist that these cells may also acquire stemness following mutational hits in spite of its short life span. The property by which terminally differentiated cell re-acquire stemness is called de differentiation. Development of stemness increases the tumorigenic, metastatic, treatment resistant properties of the tumour. Blockage of the TGF- β1 inhibits dedifferentiation and self-renewal capability of the tumour.[5]

Side Population (SP) Cells

A subset of cells enriched with both stem cell like and tumorigenic property has been identified in head and neck squamous cell carcinoma (HNSCC).7 These cells have a unique ability to efflux chemotherapeutic drugs by expressing high levels of MDR1 and ABCG2 (ATP-binding cassette (ABC) transporter family members). A strong positive correlation has been demonstrated between the percentage of SP cells and tumour aggressiveness.[8,9]

Stem Cell Niche

Niche represents the microenvironment surrounding the cancer stem cell. This niche aids in maintaining and replenishing the stem cells.[10] The location of the niche varies among tumours. In HNSCC, the stem cells reside within a 100 µm-radius of a blood vessel indicating a perivascular niche. Ablation of tumor-associated endothelial cells has resulted in a drastic reduction in CSC.[11,12] Inflammation, angiogenesis, cancer cell microenvironment and epithelial mesenchymal transition all play an additive role in conversion of normal stem cells to cancer stem cells.

2. CONCLUSION

Researchers suggest that most human cancers arise from a single clonal cell and it undergoes malignant transformation with aggressive characteristics. CSCs have a significant role in cancer initiation, progression, metastasis and recurrences. Several hypothesis suggest that the cell fusion and horizontal gene transfer play significant role in origin of CSCs. Though studies on cancer stem cells are increasing their origins remain questionable. Hence, more research studies are required to analyse the origin of CSCs, which may shed more light on cancer behaviour, as well as helps in developing novel cancer therapies.[13]

REFERENCES

1. Dionne KR, Warnakulasuriya S, Zain RB and Cheong SC. Potentially malignant disorders of the oral cavity: Current practice and future directions in the clinic and laboratory. Int. J. Cancer. 2015;136:503-15

2. Baillie R, Tan ST, Itinteang T. Cancer Stem Cells in Oral Cavity Squamous Cell Carcinoma: A Review. Frontiers in Oncology. 2017;7:112.

3. Facompre N, Nakagawa H, Herlyn M, Basu D. Stem-like cells and therapy resistance in squamous cell carcinomas. Adv Pharmacol 2012;65:235–65.

4. Bu Y, Cao D. Department of Medical Microbiology, Immunology, and Cell Biology, Simmons Cancer Institute, Southern Illinois University School of Medicine. 913 N. Rutledge Street, Springfield, IL 62794, USA. Frontiers in Bioscience. 2012;4:819-30.

5. Sinha N, Mukhopadhyay S, Das DN, Panda PK, Bhutia SK. Relevance of cancer initiating/stem cells in carcinogenesis and therapy resistance in oral cancer. Oral Oncol. 2013;49:854–862

6. Zhang Z, Filho MS, Nör JE. The biology of head and neck cancer stem cells. Oral Oncol 2012;48:1–9.

7. Loebinger MR, Giangreco A, Groot KR, Prichard L, Allen K, Simpson C, et al. Squamous cell cancers contain a side population of stem-like cells that are made chemosensitive by ABC transporter blockade. Br J Cancer 2008;98:380–7.

8. Hadnagy A, Gaboury L, Beaulieu R, Balicki D. SP analysis may be used to identify cancer stem cell populations. Exp Cell Res 2006;312:3701–10. 141.

9. Wu C, Alman BA. Side population cells in human cancers. Cancer Lett 2008;268:1–9.

10. Morrison SJ, Spradling AC. Stem cells and niches: Mechanisms that promote stem cell maintenance throughout life. Cell 2008;132: 598–611.

11. Barker N, Ridgway RA, van Es JH, van de Wetering M, Begthel H, van den Born M et al. Crypt stem cells as the cells-of-origin of intestinal cancer. Nature 2009;457:608–11.

12. Krishnamurthy S, Dong Z, Vodopyanov D, Imai A, Helman JI, Prince ME, et al. Endothelial cell-initiated signaling promotes the survival and self-renewal of cancer stem cells. Cancer Res 2010;70:9969–78.

13. Blaylock RL. Cancer microenvironment, inflammation and cancer stem cells: A hypothesis for a paradigm change and new targets in cancer control. Surg Neurol int. 2015;6:92