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REVIEW ARTICLE

Cancer Stem Cells and Its Therapeutic Application: An Overview

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ABSTRACT

Cell potency is the ability to differentiate into other cells. Stem cells are found in every organ and tissues in our body. They have the characteristics of self-renewal and differentiation to give rise to a mature type of cells making up organs and tissues. They can be totipotent, pluripotent, unipotent, and multipotent. Today, cancer stem cells (CSCs) have been gaining ground in several malignancies, such as acute myeloid leukemia, breast cancers, head and neck cancer. They also have the similar properties of tissue stem cells of self-renewal and regeneration of tissue. Gene alteration and mutation are thought to be involved in the formation of these CSCs. They may have a role in tumor metastasis and their understanding may help in the development of prognostic markers and therapeutic application.

Keywords: Cancer stem cells, Cell potency, Head and neck cancer, Stem cells.

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INTRODUCTION

Cancer, despite its recent treatment therapies, has been the most common cause of morbidity and mortality worldwide. Stem cells are being used for decades as one of the methods for cancer therapy.[1] Stem cells are undifferentiated cells, which give rise to other cells. They have two unique characteristics: The ability to self-renewal, which means that they can multiply and produce numerous cells of themselves, and the ability to differentiate, which means, it can change into two or more different types of cells. In the human body, there are many sources of stem cells, which include eye, brain, cord blood, bone marrow, skin, etc. It can be divided into embryonic (embryos; inner cell mass of blastocyst), somatic (human adult), and germinal (from primary germinal layers of the embryo) stem cells. The most common adult stem cells are hematopoietic stem cells and mesenchymal stem cells.[1]

CANCER STEM CELLS

Cancer was always the most common cause of mortality in the past and is still today. In the past few decades, stem cell biology has provided new approaches and research into cancer biology.[2-5] It is now believed that tumor cells have the stem cell properties of self-renewal and differentiation to generate mature cells. These cells are called cancer stem cells (CSCs), which have the ability to produce distinct cell types that are found in their original tumor (Flow Chart 1).[5,6] It is still unclear whether the CSCs are derived by transformation of stem cells or are due to differentiation of mature neoplastic cells.[5-8] The CSCs were actually first discovered in the hematopoietic system.[5,9,10] Cancer stem cell-rich tumors have high metastatic rate and poor prognosis as they have increased resistance to chemotherapeutic agents.[5,11-13]

It is generally accepted that cancer may arise from tissue stem cells through genetic and epigenetic changes and CSCs are recognized by the presence or absence of different cell surface markers.[14]

Cancer Stem Cells and Tumors

Cancer stem cells were first described in acute myeloid leukemia and subsequently have been identified in breast

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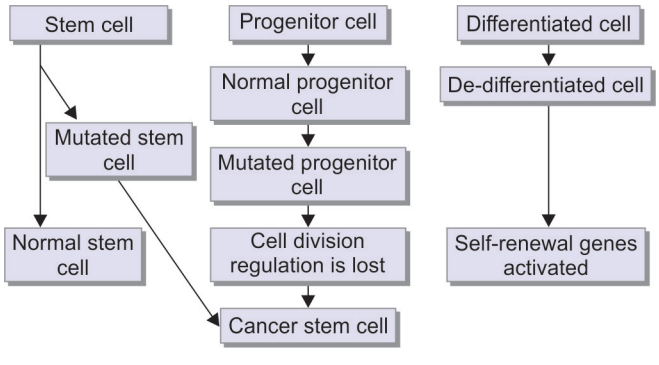
Flow Chart 1: Cancer stem cell arising from stem cell, progenitor, and differentiated cell



and central nervous system cancers, such as glioblastoma and medulloblastoma.[15] The self-renewal ability of stem cell is regulated by signals from the surrounding stem cells called niche, and the alteration in this niche signaling has been observed in human T-cell acute lymphoblastic leukemia and cervical and breast cancer. According to past literature and studies, it is proposed that breast cancers may arise from mammary stem cells that have undergone transformations or from the early progenitor cells.[16]

Head and neck cancer is the sixth most common cancer in the global population. Research on head and neck CSCs has started recently in the year 2007. Mortality rate in head and neck cancer is usually due to metastasis to lymph nodes and distant organs, and CSCs act as important purveyors of metastasis.[17-20]

Cancer Stem Cells and Therapeutic Approach

Eradication of cancer is concerned with targeting and elimination of these CSCs sparing the normal stem cells. But, there are always challenges to implementing such strategies as both share similar properties of self-renewal; however, with recent studies using animal models, these strategies can be approachable.[16] Cancer stem cells are identified, which has brought important therapeutic implications. According to Gil et al,[21] the resistance of these CSCs to chemotherapy may be caused by increased expression of proteins from the B-cell lymphoma 2 family, which actually leads to an increase in expression of membrane proteins, which are responsible for drug resistance.[21]

In tumors, CSCs play a role in three ways: Mutation of normal cells into cancer cells, ultimately leading to the primary tumor; they may also play a role in the recurrence of the tumor and can migrate causing metastasis.[1,22] Gene expression profile of CSCs is different and by comparing it with the bulk tumor population, normal stem cells, and tissues, there may be a possibility in identifying therapeutic targets that preferentially attack CSCs.[2,15,23]

Cancer stem cell biomarkers are used as a tool to identify CSCs as well as become target of many drugs developed for its cure. In recent years, many markers have been identified, which include CD133, CD44, ABCG2, and some other cell surface proteins. CD133 is a glycosylated protein used for the identification of brain tumor, lung, pancreatic, liver, prostate, colorectal, and head and neck cancers. CD44 has been used to identify cancers of the breast, pancreas, head and neck, ovarian, and colon. ABCG2 plays a role in the maintenance of stem cell phenotype and helps in identifying cancers of lung, liver, brain, prostrate, etc.[24] There are many other noncarbohydrate stem cell markers, which are also CSC markers, such as Bmi-1, CD29, CD44, CD90, CD117, Nestin.[25] Natural compounds, such as salinomycin, curcumin, sulforaphane have also been found in recent years to have the ability to kill CSCs.[24]

Cancer Stem Cells and Its Response to Chemotherapy

The response to chemotherapy becomes an issue when there is a recurrence of the tumor. The recurrent tumor may arise due to the survival of CSCs present within the primary tumor despite chemotherapy and surgical removal. There are several antineoplastic drugs available and the CSCs are protected against it by various defense mechanisms, which are CSC intrinsic and CSC extrinsic. CSC-intrinsic mechanism involves deoxyribonucleic acid (DNA) repair, expression of drug pumps, and altered cell cycle, whereas CSC-extrinsic mechanism involves the effect of tumor microenvironment on CSCs.[14,26]

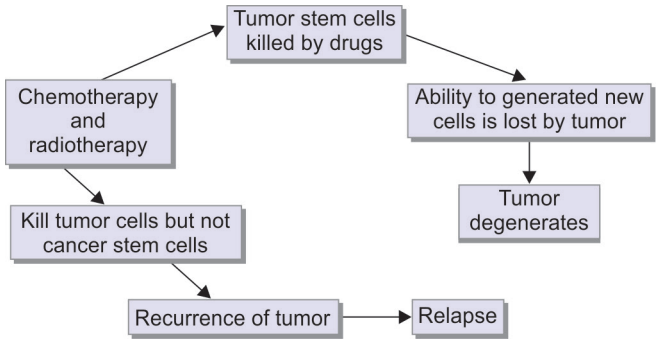
Cancer Stem Cells and Its Response to Radiotherapy

Radiotherapy either alone or in combination with chemotherapy has curative potential in head and neck cancers and other solid tumors. They also help in the control of local recurrences of the primary tumor (Flow Chart 2). According to past studies, radiotherapy involves DNA amount in both CSC and non-CSC compartments, but damage repair was more robust in CSC and non-CSC population who underwent apoptosis more after the radiation.[14,27]

Targeting CSCs and Surface Markers

Cancer stem cells are ideal for treatment of cancer by targeting cytotoxic drugs and stem cell surface markers. A specific surface marker like CD133 that is a marker of primitive hematopoietic and neural stem cells seen in hepatocellular and gastric cancer is considered as an important CSC-associated marker. According to previous reports, $CD133^+$ CDCs have strong resistance to chemotherapy and radiotherapy.[28-32]

Flow Chart 2: Cancer stem cells in response to chemotherapy and radiotherapy



CONCLUSION

Research and studies in the past suggest that tumor is formed due to the development of CSCs by deregulation of normal cells or tissue stem cells. The discovery of CSCs in various tumors has provided new approaches for the medical professions in understanding cancer biology. Its unique properties add a great promising venture toward more effective cancer treatment and improving the mortality and modality in the future.

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