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REVİEW

Stem Cell Concept in Thyroid Cancer

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ABSTRACT
The most frequently diagnosed endocrine cancer, which causes more deaths than any other endocrine cancer, is thyroid cancer. Cancer stem cells are rare cells found in tumors that can regenerate themselves, phenotypically leads to various tumor cell populations and trigger tumorigenesis. Cancer stem cells have been identified in many cancers, including thyroid cancer. Having an understanding of the molecular mechanisms which control the biology of cancer stem cells and the disease processes will help us in designing more rational targeted therapies for aggressive thyroid cancers. In this review, we aimed to present the current accepted knowledge about thyroid stem cells, information regarding the cellular origin of thyroid cancer stem cells, and the clinical results of cancer stem cells present in the thyroid gland.
KEYWORDS: Stem cell, Thyroid, Carcinoma.

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INTRODUCTION

Every year, cancer causes millions of people to die worldwide. It is among the most researched diseases in the world of science due to its high mortality rates. It is difficult to develop an inclusive, all-encompassing treatment due to its various types and differences from person to person. Cellular-treatment-based approaches in cancer treatment are getting more and more common. Many studies have been conducted using stem cells and achieving success in the cellular treatment of cancer. The ability of stem cells to regulate immune system cells and act as immune system cells has brought stem cells to an advantageous position in cancer treatment.

STEM CELL

Stem cells are special cell groups that can renew themselves and differentiate into different types of cells, thereby building tissues and organs. Stem cells are very important in understanding how tissues and organs can develop from a fertilized egg. In addition, stem cells have significant potential in the treatment of many diseases in the fields of cell trauma and tissue generation. As a result of the conducted research, it has been observed that stem cells have different properties and can be obtained from different sources. Therefore, stem cells are basically classified according to their differentiation potential and the source from which they were obtained [1,2].

Classification of Stem Cells

Considering their differentiation capacities, they are gathered in 5 main groups;

Totipotent Stem Cells: The zygote, which is formed by the fertilization of the egg cell with a sperm, has the capacity to turn into all cells that build the body.

Pluripotent Stem Cells: Pluripotent stem cells have the capacity for self-renewal by mitosis, and the ability to differentiate into all cell types derived from the endoderm, mesoderm, and ectoderm, which are the three primary germ cell layers of the early embryo.

Multipotent Stem Cells: Multipotent stem cells have the capacity for self-renewal by mitosis. They are cells that can turn into many different types of special cells in a particular tissue or organ.

Oligopotent Stem Cells: These stem cells have the capacity to differentiate into a limited cell line or tissue.

Unipotent Stem Cells: These cells are cells capable of transforming into a single type of cell.

THYROID CANCER AND ITS TYPES

Thyroid cancer is the most common malignant endocrine tumor, but its rate in all malignancies is 1%. The

incidence of thyroid cancer has been continuously increasing worldwide, with the increasing use of diagnostic imaging [3].

Malignant thyroid tumors are divided into 3 main groups:

Differentiated thyroid cancers: Papillary carcinoma; Follicular carcinoma; Hurtle carcinoma.

Medullary thyroid cancer (MTC): Sporadic (MTC); Familial (MTC).

Anaplastic (undifferentiated) thyroid cancer.

CANCER STEM CELL MODEL

The evidence which demonstrates that cancer cell populations are not homogeneous gives a new perspective to thyroid cancer as a stem cell disease. It is predicted by the cancer stem cell model that only a subset of cancer cells is capable of self-regeneration and producing progenitor cells that can regenerate and sustain tumor growth. The cancer stem cells can divide symmetrically or asymmetrically and have a lot of potential (i.e. they are capable of creating multiple cell lines). Because of this, the cancer stem cell model is an appealing way to explain the functional diversity commonly seen in thyroid cancer. However, the use of the definition as “cancer stem cells as assets that undergo differentiation, which can lead to another cancer stem cell and is differentiated tumor cancer cells, is a fully functioning model [4,5]. It remains unclear whether thyroid cancer stem cells have gained the capability to regenerate themselves through genetic mutations, or if this ability generated as a result of epigenetic changes in normal thyroid stem cells, and whether they originate from mature cells or progenitor cells within the thyroid gland. Alternatively, thyroid cancer stem cells can result from abnormal differentiation of epithelial-characterized neoplastic cells. However, thyroid cancer stem cells are likely to be heterogeneous in both function and phenotype, regardless of their origin. A critical step to develop targeted therapies is to determine if cancer stem cells will (and how they will) change between different subtypes (even in the same form) of thyroid cancer [4,6].

MATURE STEM CELLS IN THYROID CANCER

The presence of thyroid stem cell populations in mature thyroids was first assumed by the study of performed by Dumont et al., where the injection of a minimum number of cells was required for the growth of thyroid transplants in recipient animals[7].

Later, the adult stem cell population that co-expresses endodermal markers Gata-4, and HNF4a, pluripotent marker Oct-4, and TTF Pax8, has been proven to be found in the human goitrous thyroid [8]. These findings actively support the hypothesis that states a subpopulation of pluripotent stem cells exists in the goitrous thyroid [9]. It has been found in the study of Lan et al. that thyroid stem cells which are isolated from primary cultures derived from the human goitrous thyroid can differentiate into in vitro thyroid cells [10]. In their study, stem cells were isolated from primary thyroid cultures and they were embedded in a single layer, or embedded in collagen. TSH-induced cells which were in serum-enriched medium expressed Tg, NIS, Pax8, TSHR and TPO mRNA. In addition, differentiated cells which are embedded in collagen showed iodide uptake when stimulated with TSH [10].

Hoshi et al. described "side populations of cells", which shows the characteristics of stem or progenitor cells in normal mouse thyroid tissue [9].

Although it is assumed that thyroid stem cells are enough to replenish the pool of fully differentiated thyroid cells, at this moment there is no direct evidence to support this hypothesis.

CELLULAR ORIGIN OF THYROID CANCER STEM CELLS

The thyroid cancer stem cell hypothesis is stating the claim that thyroid cancer stem cells can originate from either normal stem cells, progenitor cells, or differentiated and more mature cells. While many of these claims of origin are possible, most researchers believe that the stem cells or the progenitor cells are the most likely criminals [11]). There are a large number of studies that have demonstrated that only a subset of cancer cells that exhibit features of stem cells are actually tumorigenic. For example, in the study of Al-Hajj et al., it was demonstrated that breast cancer cells can be divided into tumorigenic and nontumorigenic populations based on specific markers. In particular, CD44 + CD24 / low lineage populations can form tumors consisting of a heterogeneous cell population, similar to those obtained [12].

Later, Zhang et al. showcased a model for the origin of the four different types of thyroid carcinoma according to their levels of differentiation. Anaplastic cancer can occur directly from the stem cell because it is a poorly differentiated cancer. Well-differentiated follicular and papillary carcinomas can result from bipotential stem cells. Medullary carcinoma, which is another well-differentiated cancer, can originate from progenitor C cells [13]. Although the potential for the presence of thyroid cancer stem cells are shown by the discovery of stem cell markers in the thyroid gland, identifying these cells can be quite difficult because of the extremely low lifetime turnover in the thyroid gland. Since there is no successful treatment for anaplastic carcinoma, its cellular origin is of particular interest [11].

So far, there is no evidence that anaplastic carcinoma is caused by additional mutations to papillary carcinomas. Takano and Amino use this evidence to support their hypothesis for the origin of anaplastic carcinoma. Their opinion is that anaplastic carcinoma consists of residues of fetal thyroid cells instead of normal thyroid follicular cells before puberty and has cancer properties before the start of their division. Also, the fetal cell carcinogenesis hypothesis reveals a similar gene expression profile between fetal thyroid cells and thyroid cancer cells. However, this hypothesis needs more research before it can be considered as an explanation for anaplastic carcinoma [5,14] .

IDENTIFYING THYROID CANCER STEM CELLS

There has been a number of in vivo and in vitro strategies that were used to try and identify thyroid cancer stem cells.

In vivo strategies

Stem cells can lead to differentiated progenitors with reduced proliferative potential. The most accurate way to evaluate assumed cancer stem cells is by injecting them into animal models that lack the main elements of the immune system. Cells isolated from the resulting tumors can then be transferred to secondary and tertiary mice to determine their long-term tumorigenic and self-regenerating potential. The examination of the cellular composition of any tumor which is derived from secondary and tertiary xenografts can confirm whether these tumors regenerate the phenotypic and histological heterogeneity seen in the primary tumors [4].

Other in vivo analyzes are also required for the assessment of the metastatic activity of cancer stem cells. Studies such as these require the development of serial, orthotopic transplantation experiments. Initial reports related to cancer stem cells suggest that only a rather small subset of tumor cells can both regenerate and differentiate. However, with the development of new mouse strains for use as transplantation models suggests that these cells may not be as rare as previously thought [15,16].

In vitro strategies

There are several in vitro functional experiments which are used to evaluate thyroid cancer stem cell potential in a tissue culture dish. Thyrosphere formation experiments are included in these approaches, these are serial colony formation experiments, limiting dilution experiments, proliferation and apoptosis experiments, and differentiation experiments [4,6].

Considering that it is possible to grow normal thyroid stem cells as sphere-like cellular aggregates in a special stem cell culture medium, the thyrosphere test is the best studied sphere-based analysis to determine the multipotency and clonality of potential thyroid stem cells. Additionally, separating thyroids into single cells, limiting dilution, and then subjecting them to serial culture (which is called "passaging") can be used to evaluate the long-term proliferation potential of these cells. Since cancer stem cells are considered to be responsible for both the onset of tumor and relapse after chemotherapy, resistance to chemotherapeutic agents can be evaluated using in vitro cytotoxicity experiments and in vivo tumor growth studies [17,18].

Identification of thyroid cancer stem cells

The identification of thyroid CSCs was performed using the CSC markers which were identified in other solid and hematopoietic malignancies. In recent years, advances in flow cytometry and xenotransplantation techniques have brought great convenience in understanding the molecular pathogenesis of cancer stem cells. Especially with the help of the flow cytometry technique, cancer stem cell separation using surface markers has been widely used in recent years. For thyroid cancer stem cells, 11 candidate markers have recently been identified from eight thyroid cancer cell lines [CD13, 15, SSEA-1, 24, 44, 44v, 90, 117, 133, 166, and 326 and ALDH]. However, there are many articles reporting candidate markers for thyroid CSCs [5,19,20].

CD133 is a 117 kDa molecular weight membrane protein, used to differentiate tissue and stem cells from prostate, pancreas, kidney, brain, thyroid and colon-like tumors. It was first shown in 2003 by Singh et al. that CD133 + cell population was enriched in stem cells [21].

In the study of Tseng et al., CD133 + cells expressed their root genes (Oct-4, Sox-2 and Nanog) and drug-resistant genes (ABCG2, MDR1 and MRP), forming thyrospheres in vitro and in vivo [22].

The most commonly used stem cell separation methods are spherical generation methods, side population separation (with the help of Hoechst 33342 dye), and methods of using surface markers based on ALDH1 activity [5].

Comparison of normal thyroid stem cells and thyroid cancer stem cells

Thyrospheres are produced from nodular goiter tissue and Graves, tissues as well as normal thyroid cells. In the study of Giani et al. comparing normal thyroid SCs and thyroid CSCs, PTC-CSCs showed higher clonogenicity potential, creating more irregular and larger spheres when compared to normal SCs. PTC-CSCs also showed higher levels of stem cell markers (Sox-2, Oct-4, and ABCG2), lower levels of certain differentiation markers (Pax-8 and TTF1) and lower differentiation efficiency [5,23].

Thyroid cancer stem cells and metastasis

CSCs are capable of seeding new tumors when they are implanted into appropriate animal hosts. Considering its motility, apoptosis resistance and invasiveness, CSCs are central players in tumor recurrence and formation of metastasis. Disseminating tumor cells (DTCs) are considered to be the main cause of metastatic disease, recurrence, and chemo-resistance, and are characterized by their capacity for migration from primary tumors to secondary sites. Therefore, DTCs may exist for a long time in a dormant state, corresponding to the latent time between primary tumor detection, treatment, recurrence, and metastatic spread. The matrix metalloproteinases which are secreted by stromal cells, can in some cases induce the transition from a dormant tumor to metastatic growth, and vice versa through the formation of an allowed niche [18,24,25].

Clinical results of thyroid cancer stem cells

If it is proven to be definitely true, the cancer stem cell theory can deeply affect how we treat cancer. With the identification of cancer stem cells, a specific target for chemotherapy and drugs could be provided and this may even determine the aggressiveness of treatment. At the moment, many common protocols for chemotherapy and radiation target all multiplying cells, whether they are cancerous or not. However, if the disease is related to cancer stem cells, this may not be the correct approach. If the cancer stem cells are not active when the treatment is initiated, they can survive treatment aimed at killing multiplying cells. In that case, it may appear as if the patient made a full recovery only to come back with

recurrence years later when the cancer stem cells are reactivated. The development of medication which specifically targets cancer stem cells can make cancer treatment more efficient, more successful, and less toxic to the patient. For instance, stem cells have specific types of active ATP-binding cassette carriers which can increase the resistance of cancer stem cells to typical treatment options. Targets that are stem-cell-specific such as these can be very helpful in designing new therapies. Although the cancer stem cell hypothesis is still being studied, the effects of future treatments have the potential to be great and may even change the way we approach, diagnose, and treat the disease [4].

The possible presence of at least two different populations - one that initiates and maintains tumor growth, and another that directs metastasis – is an additional challenge in targeting thyroid cancer stem cells. These different populations can exhibit unique properties that make it difficult to kill them, both by their ability to develop drug resistance and their sensitivity to existing treatments. The prevalence of thyroid cancer stem cells, present in thyroid cancer, can also have important therapeutic effects. If the amount of thyroid cancer stem cells is really low, there may be improved treatments aimed at selectively killing this small cell subpopulation. Conversely, if thyroid cancer stem cells are present in large numbers, a new strategy may be required to target this large populations of cells which are resistant to treatment. Lastly, it will be critical to develop various analyses to measure the prevalence of cancer stem cells after treatment and to evaluate the success of these new targeted treatment regimens.

CONCLUSION

Stem cell technology has drastically changed and improved modern medicine, essentially revolutionizing it, and provided never before seen opportunities to explore molecular mechanisms that control the basic biological and disease processes. As we learn and discover more, and our understanding of the thyroid stem cell biology increases, this also increases our hope that such information will lead to more effective and safer treatment regimens for thyroid cancer than is currently available. There are many effects of the presence of thyroid cancer stem cells. Finding out if they guide the disease (and how), how they change within and between the four subtypes of thyroid cancer, and whether different types of cancer stem cells facilitate tumor formation and metastasis, will help us with drug discoveries, to more accurately define the disease processes, prevent toxicity and metastasis, and to produce new and better tests to design improved intervention strategies for this disease. Understanding the way thyroid cancer stem cells emerge can help develop mathematical models to predict cancer risk. Ultimately, studies conducted on thyroid cancer stem cells may reveal new prognostic tools and better targeted treatment strategies for anaplastic thyroid cancer, a disease that still has a poor prognosis.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

STATEMENT OF ETHICS

The authors have no ethical conflicts to disclose.

DISCLOSURE STATEMENT

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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