The Role of Mesenchymal Stem Cells Secretome in Regeneration of Thyroid Tissue Damage after Thyroid Lobectomy: A Literature Review

Abstract

Mesenchymal Stem Cells (MSC) are a type of stem cell that is multipotent and originates from the mesoderm and ectoderm at an early stage of development and can differentiate into: 1. Ectodermal derivatives such as: neurons, keratocytes and keratinocytes; 2. Endodermal derivatives such as: hepatocytes and pancreatic β cells. MSCs were first discovered in the bone marrow, but in recent research they have been found in many other body tissues, such as the lungs, pancreas, liver, adipose tissue, synovial tissue, muscles, bones, amniotic fluid and umbilical cord blood. MSCs vary in content, accessibility, proliferation ability, immunomodulatory capacity, and the cytokines they secrete, and have different therapeutic potential based on different sources. Recent evidences showed that even the secreted factor including secretome, microvesicles, or exosomes alone without the cell may repair damaged tissue in various conditions. In this review, we summarize the latest research which aims to provide an overview of the influence of the mesenchymal stem cells secretome in regenerating damaged follicular thyroid tissue after thyroid lobectomy, so that in the future research can be carried out on this matter to minimize complications after thyroid lobectomy, can even regenerate follicular thyroid tissue, and can be an option treatment to help overcome the current challenges of hormone replacement therapy.

Keywords: Mesenchymal Stem Cells, Mesenchymal Stem Cells Secretome, Follicular Thyroid Nodule, Thyroid Lobectomy

Introduction

“Mesenchymal Stem Cells (MSC) are a type of multipotent stem cell that originates from the mesoderm and ectoderm in early development and can differentiate into differentiate into: 1. Ectodermal derivatives such as: neurons, keratocytes and keratinocytes; 2. Endodermal derivatives such as: hepatocytes and pancreatic β cells” [1,

2]. “MSCs were first discovered in the bone marrow, but in recent research they have been found in many other body tissues, such as the lungs, pancreas, liver, adipose tissue, synovial tissue, muscles, bones, amniotic fluid and umbilical cord blood” [3, 4]. “MSCs vary in content, accessibility, proliferation ability, immunomodulatory capacity, and the cytokines they secrete, and have different therapeutic potential based on different sources. Recent evidences showed that even the secreted factor including microvesicles, or exosomes alone without the cell may repair damaged tissue in various conditions” [5]. Previously, there had been no research discussing the secretome regeneration potential of mesenchymal stem cells in thyroid tissue damage after thyroid lobectomy. In this review, we summarize the latest research which aims to provide an overview of the influence of the mesenchymal stem cells secretome in regenerating damaged follicular thyroid tissue after thyroid lobectomy, so that in the future research can be carried out on this matter to minimize complications after thyroid lobectomy, can even regenerate follicular thyroid tissue, and can be an option treatment to help overcome the current challenges of hormone replacement therapy.

Mesenchymal Stem Cells Secretome Characteristics

“In response to different microenvironmental conditions, MSCs produce and secrete a wide variety of bioactive molecules. MSCs are also referred to as “trophic factories”. And the secretome is a combination of all trophic factors or molecules secreted by these cells into the extracellular space” [13]. “Mesenchymal Stem Cells secretome have the ability to produce a variety of autocrine and paracrine factors including cytokines, extracellular matrix (ECM) proteases, chemokines and growth factors, thus allowing the possibility of being used as a potential source of cell-free based therapy” [6]. In addition, MSC secretome also contain exosomes and extracellular vesicles [93]. Exosomes can contain lipids, miRNAs, long noncoding RNAs that regulate various related signaling inflammation pathways [7]. Identification and characterization of all forming biomolecules secretome is difficult to achieve, but can improve understanding of the profile of secreted factors and provides information about its regulation, function, and clinical applications [8]. The MSCs can influence surrounding cells and regulate various biological processes [9]. Overall, these characteristics indicate that MSCs have potential cell therapy for

regeneration of damaged tissue with different tissue systems, such as heart, bones, kidneys, lungs, including thyroid tissue [7]. Summary information on the secretome potential of mesenchymal stem cells can be seen in **Figure 1**.

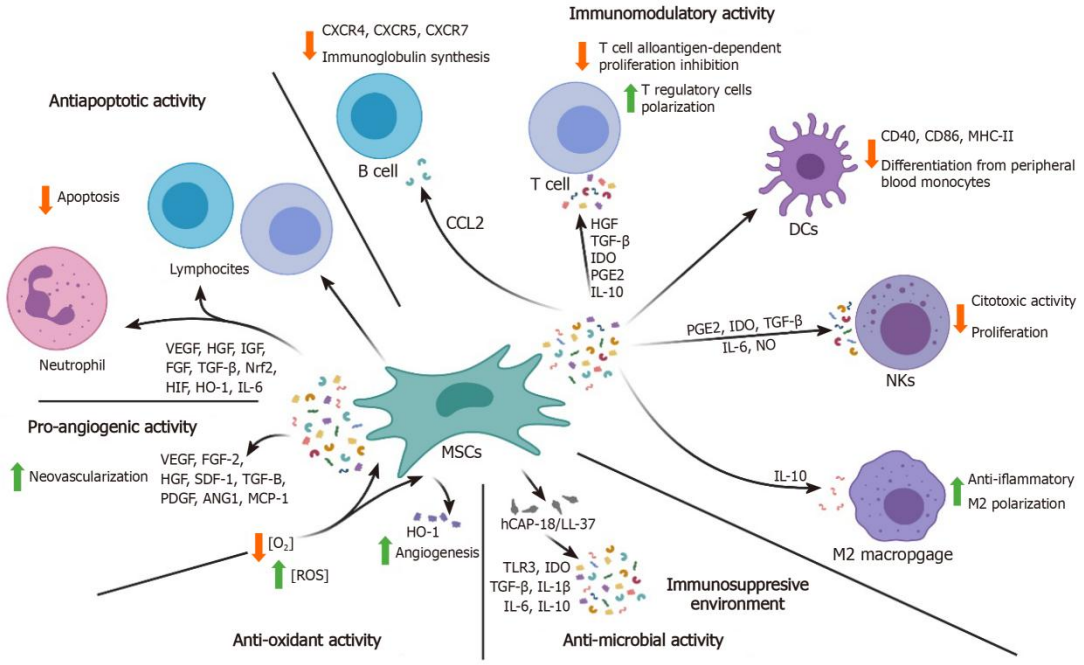

Figure 1. Potency of various soluble factors secreted by mesenchymal stem cells [6].

Thyroid Lobectomy Indications for which Mesenchymal Stem Cells Secretome can be Administered

"Indications for choosing a thyroid lobectomy or lobectomy plus isthmusectomy for thyroid nodules include oncologic outcomes, such as disease-free survival, surgical morbidity and long-term treatment effects. Thyroid lobectomy has a lower complication rate than total thyroidectomy. In a meta-analysis study it was found that the combined risk of postoperative complications for total thyroidectomy versus thyroid lobectomy was 10.67 in 50,445 patients. Among the relative risks found were temporary recurrent nerve palsy of 1.69, permanent recurrent nerve palsy of 1.85, and hematoma of 2.58, while the relative risk of temporary hypocalcemia was 3.1 and permanent hypocalcemia was 1.69" [10].

“The advantages of thyroid lobectomy, combined with a large body of data confirm the excellent survival of patients with low-risk cancers treated with lobectomy. This has led to a shift towards lobectomy” [11]. “In a review outlined the therapeutic potential of mesenchymal stem cells in regenerating thyroid cells and modulating thyroid function. Mesenchymal stem cells represent a promising form of treatment for thyroid disorders” [12].

Potential Regeneration of Mesenchymal Stem Cells Secretome in Thyroid Tissue Damage

“Although research on the secretome regenerative potential of MSCs is still rare compared to research on the regenerative potential of MSCs, the results of preclinical trials that have been carried out to date have shown significant positive results and minimal side effects associated with the use of this product. MSCs have a role as the main trigger of regenerative activity which represents the main components of the soluble and vesicular parts as well as the main biological processes in tissue regeneration” [13].

In recent research, MSCs were shown to secrete interleukin 1 receptor antagonist (IL-1Ra) which is a competitive inhibitor of Interleukin-1 (IL-1). Production of IL-1Ra induces inhibits B cell differentiation and M2-like macrophage polarization [14] and in vitro stops the production of TNF-α by macrophages [15]. “Growth factors including VEGF (vascular endothelial growth factor), LIF (leukemia inhibitory factor), and HGF-1 (hepatocyte growth factor-1) are also contained in the secretome which have potential as regenerative agents” [15].

“Many studies have proven that there is a synergistic action of small molecules secreted by MSCs that can reduce cell injury and increase tissue repair capacity” [25, 26]. “The proximity of the host cell is not necessary because the soluble molecules are carried to the target cells. Therefore, the secretome of MSCs, including extracellular vesicles (EVs) derived from MSCs (MSC-EVs), is of more interest than MSC transplantation itself. EVs represent an intercellular communication system, which is used by many types of cells capable of carrying many molecules in one package to specific target cells, so they can be useful in therapy”**(Figure 2**) [27, 29]. “The medical applications of vesicles change along

with the composition and structure of the stem cells [20]. In this regard, MSC-EVs represent a powerful regenerative agent capable of maintaining or restoring tissue homeostasis" [28]. Several studies suggest that the secretome of mesenchymal stem cells has regenerative potential against tissue damage. The regenerative potential of the secretome of mesenchymal stem cells against more specific thyroid tissue damage still requires further review and experimental research for use in clinical therapy.

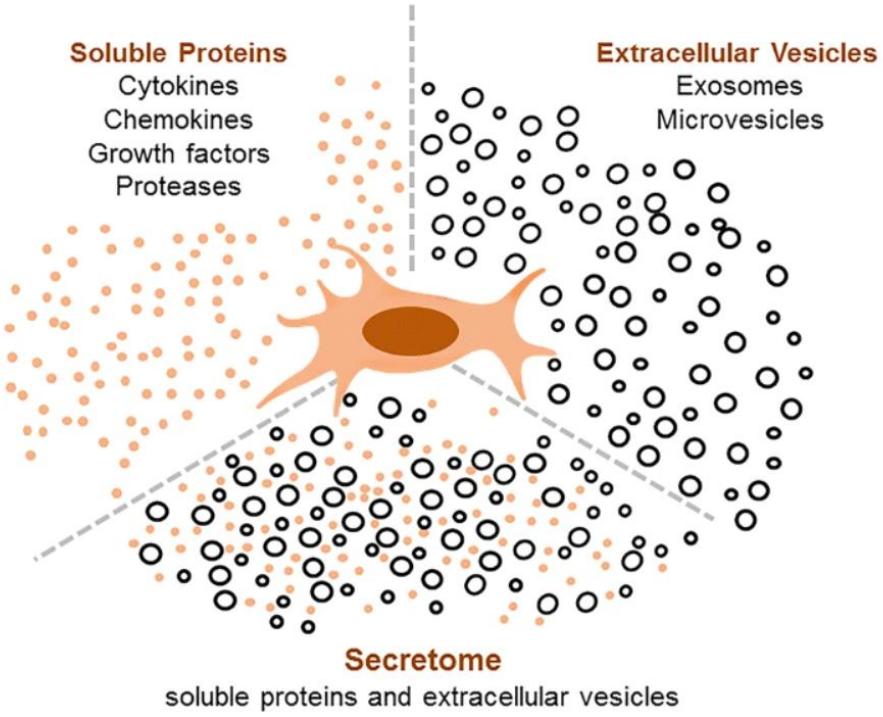

Figure 2.MSC secret overview. The secretome consists of soluble proteins that include biologically active factors and secreted extracellular vesicles. Biologically active factors such as the cytokine interleukin 10, tumor necrosis factor-α, chemokine eotaxin-3, and hepatocyte growth factor and transforming growth factor-β isoform 3. Vesicular factors include exosomes and microvesicles [29].

Clinical and Experimental Trials

Based on recent findings, researchers and physicians have shifted their therapeutic paradigm from passive reduction of tissue damage to active improvement in tissue regeneration and function. Although for almost two decades cell-based therapy was considered a philosopher's stone for enhancing tissue regeneration, this concept began to falter after the research of Gnecchi et al. in 2005 [16] that one of the first groups to show that paracrine factors present in the secretome released from mesenchymal stem

cells are capable of promoting tissue regeneration. In subsequent years, subsequent studies from around the world supported the hypothesis that paracrine factors, rather than cellular factors, were indeed responsible for the beneficial effects [17-21].

“The secretome of mesenchymal stem cells consists of factors that are actively and passively released from the cell and contains various soluble proteins including cytokines, growth factors, chemokines, free nucleic acids, lipids, and extracellular vesicles (EVs). Extracellular vesicles can be subdivided based on size, density, surface markers and origin into apoptotic bodies, microparticles and exosomes. In recent times, exosomes have become the focus of research based on their high capacity to interact with target cells and their ability to selectively modify cell signals” [22]. “One article has summarized and discussed the role of EVs in the recent field of tissue regeneration and regenerative medicine” [23]. Currently there is no review or clinical research regarding the role of Secretome mesenchymal stem cells in regenerating damaged thyroid tissue after thyroid lobectomy.

“In recent decades, thyroid lobectomy has been associated with the influence of decreasing levels of endogenous thyroid hormone or exogenously administered thyroid hormone on enzymatic activity/function, or levels of molecules regulated by thyroid hormone in the brain, hypothalamus, pituitary and liver. In another study, a quantitative analysis of thyroid function after inoculating thyroid cells into rodents undergoing thyroid lobectomy/total thyroidectomy and its relationship with neoplasms was carried out” [24].

“In a study using a mouse model to analyze thyroid regeneration after thyroid lobectomy, the morphology and gene expression of the remaining tissue/cells were carried out. In this study, thyroid lobectomy was performed to remove the entire thyroid lobe and ~2/5 of the tail segments of the other lobe. During this study, it was noted that the central area of both thyroid lobes (without thyroid lobectomy) served as a center of proliferation where many immature microfollicles, and bromodeoxyuridine (BrdU)-positive and/or C cells were located. One week after thyroid lobectomy, serum TSH levels increased drastically, resulting in goitrogenesis, which almost completely resolved within 2 weeks after thyroid lobectomy. At that time, a marked increase in the number of BrdU-positive

cells and cells with clear or faint eosinophilic cytoplasm was seen in the central area and areas continuing to the edge of the incision. Some positive clear cells showed active proliferation and expressed Foxa2 as a definite endoderm lineage marker for BrdU cells. Microarray and pathway analysis showed that the expression of genes involved in embryonic development and cancer was affected by thyroid lobectomy. Electron microscopy shows that clear cells are scanned in the cytoplasm, and retain features reminiscent of C cells that have dense neuroendocrine granules or follicular cells juxtaposed to the lumen with microvilli. Overall, clear cells may be C cells or follicular cells, which are immature clear cells that play a role in repair, regeneration of the thyroid gland, and/or goitrogenesis after thyroid lobectomy" [24].

Future Direction

The limited experimental research and even the absence of clinical research on the potential for regenerating the secretome of mesenchymal stem cells against damage to thyroid follicular tissue after thyroid lobectomy, is a challenge for researchers in the future. The author hopes that this review can be used as a basic for future experimental research and can be developed into clinical research.

Conclusion

In conclusion, MSCs produce a large number of bioactive molecules and extracellular vesicles, known as the secretome having important paracrine effects on surrounding cells and tissues. The use of MSC secretomes in tissue regeneration therapy would avoid the problems associated with MSC-based therapies, such as low cell viability and engraftment, which importantly limit their therapeutic efficacy, or the downsides and effects associated with administration of these cells. In the case of administering MSC secretome to damaged thyroid tissue after thyroid lobectomy, it is possible to become a regenerative agent in this condition. Many studies state that the MSC secretome has regenerative potential in tissue damage. The author hopes that there will be research regarding the administration of MSC secretome to post-operative tissue damage, especially to thyroid tissue damage after thyroid lobectomy, to develop insight into MSC-based regenerative therapy.

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