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Review

Stem Cell Applications: A Promising Future for Autoimmune Diseases?

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ABSTRACT

Autoimmune diseases are a group of conditions characterized by a mistakenly immune response against the body's own tissues. Although there are over 100 different types of autoimmune diseases, some of the most well-known examples include diabetes mellitus, rheumatoid arthritis (RA), and multiple sclerosis (MS). While the exact pathogenesis of these diseases is not yet fully understood, current treatment methods are mostly palliative and can cause unwanted side effects without offering a cure. Stem cell (SC) applications, on the other hand, offer a promising alternative for the treatment of autoimmune diseases. Stem cells are not only unspecified and pivotal cell types present in tissues and organs, but also they can be regenerated and differentiated into any other cell types according to the needs of the body. Several types of SCs have been investigated for their potential use in autoimmune diseases, including induced pluripotent stem cells, embryonic stem cells, mesenchymal stem cells, and hematopoietic stem cells. These SCs have revolutionized biomedical applications in autoimmune disorders due to their immunomodulatory effects despite some conflicts about their biology, safety, and manipulation in applications before their use as therapeutic agents. In this chapter, we not only cover some common autoimmune diseases such as diabetes, RA, MS, systemic lupus erythematosus, and Graves' disease but also examine potential SCs applications in detail, as well as discuss whether they can be cutting-edge therapy and a turning point in autoimmune diseases compared to conventional methods. Additionally, current methodologies of using SCs in autoimmune diseases are examined, and future perspectives are highlighted to further explore this promising field.

Keywords: Autoimmune diseases, immune response, immune system, stem cells, treatment.

Stem cells are undifferentiated cells that can develop into different types of cells in the body. They are typically divided into two main categories: embryonic stem cells (ESCs) and adult stem cells (ASCs). Embryonic stem cells are derived from the inner cell mass of a developing embryo, while ASCs are found in various tissues throughout the body. Stem cells can be further categorized based on their origin or structure.[1] Structurally, they can be classified as totipotent, pluripotent, or multipotent depending on their ability to differentiate into different cell types. While totipotent SCs can differentiate into any cell type in the body, including extra-embryonic cells, pluripotent SCs can differentiate into any cell type except for extra-embryonic cells. On the other hand, multipotent SCs can differentiate into a limited range of cell types.[2]

Stem cells possess several important characteristics, including self-renewal and the ability to differentiate into different cell types. They also can regenerate damaged tissues in the body, making them an important tool for regenerative medicine. Stem cells are used in various medical procedures, such as bone marrow transplants, and have the potential to treat a wide range of diseases, including cancer, cardiovascular disease, and neurodegenerative disorders. Stem cells also have unique properties such as the ability to proliferate, differentiate, and migrate to injured sites to promote tissue repair and regeneration.[3] They are found in various tissues in the body, such as bone marrow, adipose tissue, and umbilical cord blood. Due to their regenerative potential, SCs have been used

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in various therapeutic applications, including tissue engineering, drug discovery, and disease modeling. The most commonly used SCs for therapeutic purposes are mesenchymal stem cells (MSCs), which can be easily obtained from adipose tissue and bone marrow. Mesenchymal stem cells are easy to isolate and have been studied extensively due to their potential use in tissue regeneration. They have been shown to have immunomodulatory effects, which make them an attractive tool for treating autoimmune diseases.[4] On the other hand, induced pluripotent stem cells (iPSCs), which are generated by reprogramming somatic cells, have emerged as a promising source of patient-specific stem cells for personalized medicine.[5] Moreover, while ESCs have the potential to differentiate into any cell type in the body, their use is controversial due to ethical concerns. No matter what type of SCs are used, they all show unique characteristics and can fulfill different functions in the body. Furthermore, they hold great promise for medical treatments and further research is necessary to fully understand their potential and limitations.[6] From the point of view of autoimmune diseases, tissue regeneration, anti-inflammatory and immunoregulatory properties of SCs are utilized. Thus, in this review, after examining these properties of SCs, autoimmune diseases will be closely examined and recent studies will be given.

TISSUE REPAIR FUNCTIONS OF STEM CELLS

Stem cells have the unique ability to differentiate into a wide variety of cell types, making them critical for tissue repair and regeneration. Stem cells are capable of self-renewal, meaning that they can divide and produce identical copies of themselves, as well as differentiation, which is the process by which they develop into specialized cells with specific functions. In tissue repair, SCs play several important roles.[3,7]

One of the most significant is their ability to replace damaged or lost cells in tissues, such as in the case of injury or disease. For example, in the skin, SCs located in the hair follicles and sebaceous glands can differentiate into various skin cells, including epidermal cells, which can then migrate to the site of injury and contribute to the repair process. In addition to replacing lost or damaged cells, SCs also produce factors that promote tissue repair and regeneration. These factors, which are known as paracrine factors, include growth factors, cytokines, and chemokines, and they can stimulate the proliferation and differentiation of other cells in the tissue.[8] The other significant feature of SCs that they can also modulate the immune response, which is critical for tissue repair and regeneration. During tissue injury, the immune system is activated to remove damaged cells and debris and to initiate the repair process. Stem cells can regulate this immune response by releasing anti-inflammatory factors, which can help to reduce inflammation and promote tissue repair. Stem cells have also been shown to play a role in the formation of new blood vessels, a process known as angiogenesis. This is particularly important in tissues with poor blood supply, as it can help to improve oxygen and nutrient delivery to the tissue and promote healing.[9]

ANTI-INFLAMMATORY EFFECTS OF STEM CELLS

Stem cells are known for their ability to differentiate into various cell types and contribute to tissue regeneration and repair. In addition, SCs also possess anti-inflammatory properties, which can be beneficial for various conditions associated with inflammation.[10] From an immunological standpoint, SCs can regulate the immune response by modulating the activity of immune cells such as T cells, B cells, and macrophages. For example, MSCs have been shown to suppress T cell proliferation and cytokine production, which can reduce inflammation. Additionally, MSCs can induce the production of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which can further dampen the immune response. This regulatory effect of SCs on the immune system is particularly relevant in autoimmune diseases.[11]

Stem cells also secrete various factors that have anti-inflammatory effects. Mesenchymal stem cells secrete factors such as prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), and heme oxygenase-1 (HO-1), which can inhibit the activity of inflammatory cells and promote tissue repair. Prostaglandin E2 has been shown to inhibit the activity of T cells and B cells, as well as promote the differentiation of regulatory T cells, which have anti-inflammatory properties. Indoleamine 2,3-dioxygenase has been shown to suppress the activity of T cells and macrophages and promote the activity of regulatory T cells. Heme oxygenase-1, on the other hand, has been shown to have antioxidant and anti-inflammatory effects and can promote tissue repair. The anti-inflammatory effects of SCs have been investigated for a variety of conditions such as RA and MS. Similarly, MSCs have been shown

to reduce inflammation and promote tissue repair in models of inflammatory bowel disease (IBD).[12] For instance, the study by Liang et al.[13] evaluates the use of allogeneic (immune incompatible) MSC transplantation in seven patients with refractory IBD. In the study, allogeneic MSC transplantation was performed in seven patients and the safety and efficacy of the treatment were examined. In the study, it was found that there was a significant improvement in the symptoms and intestinal inflammation of the patients after MSC transplantation. Improvement in bowel function and clinical remission (regression of symptoms) were achieved. In addition, positive effects were observed in immune system regulation and reduction of inflammation after MSC transplantation. As a result of the study, it is stated that allogeneic MSC transplantation may be a promising treatment option in refractory IBD patients and may help control intestinal inflammation with immune system modulation.

Stem cells also can directly replace damaged or dysfunctional cells, which can contribute to the resolution of inflammation. For example, in conditions such as osteoarthritis and RA, the joint tissues can become inflamed and damaged, leading to pain and loss of function. Mesenchymal stem cells have been shown to differentiate into cartilage and bone cells, which can help to repair the damaged joint tissue and reduce inflammation.[14] Stem cell therapies have shown promise for treating a range of inflammatory conditions, although further research is needed to fully understand their mechanisms of action and optimize their use in the clinic.

IMMUNOREGULATORY EFFECTS OF STEM CELLS

In addition to the ability to promote tissue regeneration and repair of SCs, they have also demonstrated immunoregulatory effects. Stem cells have been shown to modulate the immune system by inhibiting the activation of T cells, B cells, and natural killer (NK) cells, as well as the production of pro-inflammatory cytokines.[15]

Stem cells can also activate regulatory T cells, which play a crucial role in maintaining immune tolerance and preventing autoimmune diseases. These immunoregulatory effects are mediated by different molecular mechanisms, including the secretion of cytokines, chemokines, and growth factors that can influence immune cell behavior. Stem cells can also express specific cell surface molecules that interact with immune cells and modify their function. This immunoregulatory capacity of SCs has important implications for developing new therapies for autoimmune diseases and transplantation.[16]

Hematopoietic stem cells (HSCs), which are responsible for the formation of blood cells, are a significant source of immune cells, including T cells, B cells, natural killer cells, and dendritic cells. Immune cells derived from SCs have specialized functions and could potentially be used in the treatment of diseases. Therefore, SC research continues to be a promising field for developing treatments for immune system disorders.[17]

Studies have also been conducted to demonstrate the immunoregulatory properties of SCs and the extracellular vesicles (EVs) released from them. For this purpose, the study of Xie et al.[18] deals with the immune regulatory effects of stem cell-derived EVs on immune cells. Extracellular vesicles are small vesicles secreted from various cell types and play an important role in biological signal transduction. In the study, it is stated that EVs derived from SCs have various immune regulatory effects on immune system cells. These vesicles contain various biomolecules (eg, proteins, nucleic acids) that can affect the functions of the immune system. The study also examines the molecular mechanisms of the effects of EVs on immune cells. These mechanisms include factors such as signaling pathways, gene expression regulation, and microRNA transfer. Through these mechanisms, it has been shown that EVs can affect the functions of immune cells and regulate immune responses.

T Cells

T cells, or T lymphocytes, are a type of white blood cell that originates in the bone marrow and mature in the thymus gland. They are crucial for cell-mediated immunity and are central to coordinating immune responses against intracellular pathogens, cancer cells, and other abnormal cells. T cells recognize foreign antigens presented by antigen-presenting cells (APCs) via their T cell receptors and can differentiate into various effector subsets, including helper T cells, cytotoxic T cells, and regulatory T cells.[19]

T cells derive from HSCs and differentiate into different T cell subtypes through various differentiation pathways. They migrate from the bone marrow to the thymus, where they undergo positive and negative selection to ensure their functional fitness and prevent autoimmunity. T cells complete their maturation process in the thymus, where they learn to distinguish between self and

non-self antigens. The thymus provides a specialized microenvironment that supports the maturation and selection of T cells.[17,19]

B Cells

B cells are a type of white blood cell that undergo differentiation in the bone marrow and can give rise to plasma cells responsible for antibody production. Antibodies are proteins that recognize and bind to specific antigens, marking them for elimination by other immune cells. B cells are essential for humoral immunity, which involves the production of antibodies to neutralize pathogens and toxins present in body fluids. B cells are a group of cells that arise from HSCs and mature in the bone marrow. They are capable of recognizing foreign antigens and generating antibodies that can neutralize infectious agents and toxins. The maturation of B cells and the production of antibodies occur in a specialized microenvironment provided by SCs.[19,20]

Natural Killer Cells

Natural killer cells are a type of innate immune cell that can rapidly respond to infected or abnormal cells without prior exposure or antigen recognition. They are particularly effective against virus-infected and tumor cells, and they can kill target cells directly by releasing cytotoxic granules or activating death receptor pathways. Natural killer cells derive from HCSs, which play an essential role in the formation and regulation of these specialized immune cells.[21]

Dendritic Cells

Dendritic cells (DCs) are specialized APCs that capture and present antigens to T cells, thereby initiating and regulating adaptive immune responses. Dendritic cells are capable of sensing and responding to various stimuli such as pathogens, danger signals, and cytokines. Upon activation, DCs undergo maturation and migration to lymphoid organs, where they activate T cells and promote immune tolerance or immunity. Dendritic cells derived from HSCs mature in the bone marrow and other lymphoid organs, and they play a crucial role in regulating the differentiation and activation of various T cell subtypes. Stem cells are also involved in the regulation of the formation and function of DCs, which highlights their importance in the immune system.[19,20]

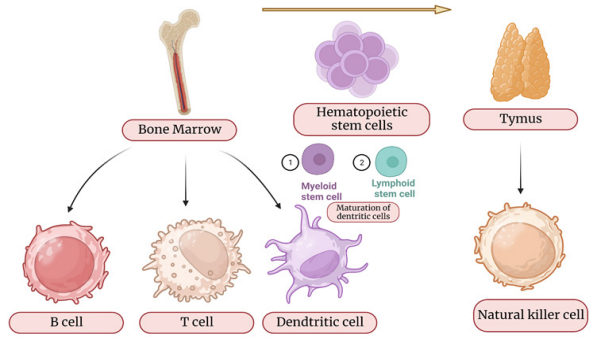

Figure 1. Immune cells and their formation

OVERVIEW OF AUTOIMMUNE DISEASES AND THEIR IMPACT ON BODY

Autoimmune diseases are a group of diseases that occur as a result of the immune system's mistakenly attack against its own cells or tissues in the body, which are normally recognized as self for protection. Although the exact cause of these diseases is not known, it is believed to result from a combination of genetic predisposition and environmental factors. Especially, genetic predisposition plays a significant role in the development of autoimmune diseases.[22]

Certain genetic variations can lead to functional changes in immune system cells or alterations in antigen presentation, increasing susceptibility to autoimmune diseases.

The pathogenesis of autoimmune diseases involves a complex interplay of cellular and molecular events that disrupt one or more of the body's natural processes. This includes antigen presentation, T cell activation, and autoantibody production. [23] Antigen presentation involves presenting antigenic peptides to immune cells and is carried out by immune system cells. In autoimmune diseases, antigenic peptides from pathogens and normal tissues can be presented, leading to the immune system attacking normal tissues as well. For example, type 1 diabetes (T1D) develops as a result of an autoimmune reaction to the insulin produced by the beta cells of the pancreas. This reaction occurs through antigen presentation and results in the activation of T cells and the production of autoantibodies.[24]

T cell activation occurs after antigen presentation and can produce antibodies directly or indirectly to attack cells in the target tissue. In autoimmune diseases, T cells can attack normal tissues and cause damage. In MS, for instance, central nervous system (CNS) damage occurs due to the attack of T cells against the myelin sheath. Another type of

autoimmune disease is antibody-mediated, where the body produces antibodies against its own tissues, which include RA and lupus. In systemic lupus erythematosus (SLE), autoantibodies are formed against nuclear components, causing severe inflammation and tissue damage.[25]

Graves' disease (GD) is also an autoimmune disease associated with autoantibody production, causing the thyroid gland to be stimulated and produce an excess of thyroid hormone, leading to hyperthyroidism. There are over 100 autoimmune diseases that have been defined, but in this review, we will focus on examining specific autoimmune diseases in detail and evaluating therapeutic studies involving SCs.

Diabetes Mellitus

Diabetes mellitus is a condition that arises when the pancreas fails to produce enough insulin, or the body becomes resistant to insulin's effects. Insulin is a hormone that facilitates glucose uptake by cells after the digestion of carbohydrates and other nutrients. Excess glucose can be stored in cells for later use. Unfortunately, diabetes causes hyperglycemia, leading to a range of negative effects on various body systems, including the nervous, cardiovascular, visual, and urinary systems.[26] For instance, diabetes can result in peripheral neuropathy, a condition that causes tingling, numbness, and pain in the hands, arms, feet, and legs. It can also damage the autonomous nervous system, leading to urinary incontinence, sexual dysfunction, and digestive issues. Cardiovascular disease risk also increases due to high blood sugar levels damaging blood vessels, along with additional factors such as high blood pressure, high cholesterol, and obesity.[27]

Diabetes can cause vision loss through diabetic retinopathy, where retinal blood vessels become damaged, and diabetic macular edema, which causes swelling affecting central vision. Diabetic nephropathy, on the other hand, leads to kidney damage that affects blood filtration, among many other associated health issues like slow wound healing, skin infections, and an increased risk of infection.[26-28]

The molecular mechanisms behind diabetes are multifaceted, with numerous stages involved, including insulin production, secretion, circulation, and perception. Diabetes is categorized into two main types. Type 1 diabetes occurs due to an autoimmune attack on pancreatic beta cells that produce insulin, leading to their death and decreased insulin production. In contrast, Type 2 diabetes (T2D) generally results from increasing insulin resistance with age. In T2D, the pancreas still produces insulin, but cells do not respond to insulin, preventing glucose from entering cells.[29]

Type 2 diabetes is also associated with factors such as weight gain, sedentary lifestyle, dietary habits, and genetic factors. However, a recent study suggested that T2D could contain autoimmune components, causing insulin resistance and beta-cell loss, which can contribute to the disease's pathogenesis. Autoimmune components of diabetes include autoimmune cells, autoantibodies, and inflammatory cells that can destroy beta cells, leading to the progression of diabetes.[30]

Improving our understanding of the molecular mechanisms of diabetes is crucial in developing effective prevention and treatment methods. Thus, diabetes research is essential for better understanding the disease's mechanisms and developing more effective treatments. In one study by Bilginer et al.[31] the presence of organ-specific autoimmune markers in T1D adult patients was examined. They found that thyroid peroxidase antibody, thyroglobulin antibody, and adrenal cortex antibody were present at a higher rate in T1D patients than in the control group. However, glutamic acid decarboxylase antibodies were similar in both groups. The study is significant in the early diagnosis and treatment of organ-specific autoimmune diseases in T1D patients. Additionally, Nederstigt et al.[32] found that T1D can accompany other autoimmune diseases such as Hashimoto's thyroiditis, GD, Addison's disease, pernicious anemia, vitiligo, RA, MS, and SLE. By reviewing 48 studies, they discovered that people with T1D had an overall 22% risk of developing other autoimmune diseases. Hashimoto's thyroiditis, GD, Addison's disease, and vitiligo were more common in T1D patients, as were multiple linked autoimmune diseases. This information is essential in monitoring T1D patients and aiding in the early diagnosis of other autoimmune diseases.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease characterized by CNS inflammation and demyelination. Although the exact cause of MS is not known, it is thought to occur as a result of the interaction of genetic predisposition and environmental triggers.

Molecular mechanisms of MS include antigen presentation that triggers the autoimmune response, T cell activation, and neurotoxicity. MS causes the

destruction of the myelin layer in the brain and damage to neurons. In this process, T cells, the precursors of the autoimmune response, respond to antigens in the brain and promote the activation of B cells in the cerebrospinal fluid.[33] This results in the production of antibodies and the continuation of the autoimmune response. The role of environmental factors in triggering the autoimmune response of MS is also evident. Low vitamin D levels, smoking, infections, and other environmental factors can increase the risk of MS. However, an interesting study by Stys et al.[34] discussed whether the disease of MS is an autoimmune disease or an autoimmune reaction. MS is a neurological disease that results from an incorrect immune response against nervous system cells. For MS to be considered an autoimmune disease, a specific autoantigen must be identified. Autoantigens are molecules that initiate the immune system's non-response against normal tissues and are antigenic components of targeted tissues. However, the identification of a specific autoantigen in MS is challenging due to the heterogeneity of the disease and the difficulty in obtaining relevant tissue samples. However, there is also evidence that MS occurs through autoimmune reactions. Autoimmune reactions are the incorrect response of the immune system to antigens found in normal tissues.

In addition, there are studies conducted to investigate the pathogenesis of MS.[35] The effect of Interleukin 6 (IL-6) and Interleukin 10 (IL-10) cytokines involved in the pathogenesis of MS was investigated in the study conducted by Ireland et al.[36] The researchers noted that IL-6 and IL-10 cytokines are produced in several different cell types and affect different aspects of the immune system. Mice were exposed to an antigen called myelin oligodendrocyte glycoprotein (MOG) and then exposed to the cytokines IL-6 or IL-10. The brains and spinal cords of the mice were then examined to measure the degree of neurological damage. Researchers have shown that IL-6 cytokine plays an important role in the pathogenesis of autoimmune diseases such as MS. IL-6 enhanced the autoimmune response and increased neurological damage. On the other hand, IL-10 cytokine has been shown to suppress the autoimmune response and reduce neurological damage.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects the joints, causing inflammation and damage. It is characterized by the infiltration of immune cells into the synovial membrane, which lines the joint space, leading to the release of inflammatory cytokines and the destruction of cartilage and bone. The exact cause of RA is not fully understood, but it is thought to result from a combination of genetic and environmental factors as well as other diseases. Some genetic variations, such as those in the HLA gene, are associated with an increased risk of developing RA.[37]

The molecular mechanisms underlying RA involve a complex interplay between various immune cells, cytokines, and signaling pathways. The initial trigger for RA is thought to be the presentation of an antigen, such as a bacterial or viral protein, by APCs to T cells. This results in the activation of T cells and the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), IL-1, and IL-6, which promote the infiltration of immune cells into the synovial membrane. The infiltrating immune cells, such as macrophages and T cells, then produce additional cytokines, chemokines, and proteases, which further contribute to joint inflammation and damage. These immune cells also interact with fibroblast-like synoviocytes, which are specialized cells in the synovial membrane that produce additional cytokines and enzymes that contribute to joint destruction.[38,39]

In addition to joint inflammation, RA can also affect other organs, such as the lungs, heart, and blood vessels, leading to a variety of symptoms and complications. RA is diagnosed based on a combination of clinical symptoms, laboratory tests, and imaging studies. Treatment typically involves a combination of medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and biologic agents that target specific cytokines or immune cells.[40]

Systemic Lupus Erythematosus

Systemic lupus erythematosus, commonly known as lupus, is an autoimmune disease that can affect various organs and tissues in the body, including the skin, joints, kidneys, heart, and lungs. It is a chronic and complex disease with a range of symptoms and severity that can flare up and subside over time. The exact cause of SLE is unknown, but it is believed to be a result of a combination of genetic, environmental, and hormonal factors. Genetic factors play a significant role in the development of SLE, and certain genetic variations can increase susceptibility to the disease.[41,42] Environmental factors, such as exposure to ultraviolet light, infections, and certain drugs, can trigger the onset or exacerbation of SLE in

genetically susceptible individuals. Hormonal factors, such as estrogen, also play a role, as women are more likely to develop SLE than men, and the disease often worsens during pregnancy.

In SLE, the immune system attacks the body's own tissues, causing inflammation and tissue damage. The exact molecular mechanisms underlying this autoimmune response are complex and not fully understood, but they involve multiple components of the immune system. One key factor in the development of SLE is the production of autoantibodies, which are antibodies that target the body's own cells and tissues. Autoantibodies are formed against nuclear components, such as DNA and RNA, and other cellular components, such as phospholipids and ribosomes. These autoantibodies can form immune complexes that deposit in tissues, leading to inflammation and tissue damage.[43]

Another key factor in SLE is the dysregulation of T cells, which are a type of white blood cell that plays a central role in coordinating immune responses. In SLE, T cells can become hyperactivated and attack the body's own tissues. In addition, regulatory T cells, which normally help to suppress immune responses and prevent autoimmune reactions, are often impaired in SLE, further contributing to the autoimmune response. Systemic lupus erythematosus is diagnosed based on a combination of clinical symptoms, laboratory tests, and imaging studies. Treatment typically involves a combination of medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressive drugs, to manage symptoms and prevent flares.[44]

Graves' Disease

Graves' disease is an autoimmune disorder that affects the thyroid gland, leading to the overproduction of thyroid hormones, a condition known as hyperthyroidism. It is caused by the production of autoantibodies, known as thyroid-stimulating immunoglobulins (TSIs), which bind to and activate the thyroid-stimulating hormone (TSH) receptor on the thyroid gland, leading to the overproduction of thyroid hormones.[45] The molecular mechanisms underlying GD involve a complex interplay of genetic and environmental factors. Genetic predisposition plays a role in the development of GD, with certain genetic variations increasing susceptibility to the disease. Environmental factors, such as infections and stress, can trigger the onset of the disease in susceptible individuals. In GD, TSIs stimulate the TSH receptor on the thyroid gland, leading to the overproduction of thyroid hormones, which can cause a range of symptoms, including weight loss, tremors, increased heart rate, and anxiety. The excess thyroid hormones can also affect various organs and tissues, leading to ophthalmopathy, a condition characterized by bulging eyes, double vision, and eye irritation.[46]

The immune system plays a crucial role in the pathogenesis of GD. Thyroid-stimulating immunoglobulins are produced by B cells, a type of white blood cell, in response to the presence of foreign antigens that resemble the TSH receptor. The TSIs then bind to and activate the TSH receptor, leading to the overproduction of thyroid hormones. Current treatment options for GD aim to reduce the production of thyroid hormones, alleviate symptoms, and prevent complications. Antithyroid medications, such as methimazole and propylthiouracil, can help reduce the production of thyroid hormones. Beta-blockers can help alleviate symptoms such as rapid heartbeat and tremors. In some cases, radioactive iodine therapy or surgery may be necessary to remove the thyroid gland.[47]

THE POTENTIAL OF STEM CELLS FOR TREATING AUTOIMMUNE DISEASES

The potential of SCs for treating autoimmune diseases has garnered significant interest from both the medical community and patients alike. Autoimmune diseases can lead to a wide range of symptoms and can be a debilitating and chronic condition. Current treatments for autoimmune diseases involve immunosuppressive drugs, which can have significant side effects and may not effectively control the disease. On the other hand, SCs have shown great potential in treating autoimmune diseases as they have the ability to differentiate into various cell types and can help to regenerate damaged tissues.[48] The use of SCs in treating autoimmune diseases is a relatively new area of research, but early studies have shown promising results.

One of the most commonly used types of SCs in treating autoimmune diseases is MSCs.. These cells have the ability to differentiate into various cell types such as bone, cartilage, and muscle cells. Additionally, they have been shown to have immunomodulatory properties, which means they can help to regulate the immune system's response and reduce inflammation. Studies have shown that MSCs can be effective in treating various autoimmune diseases such as MS, RA, and SLE.[49] For instance, the study by Liang et

al.[50] deals with a long-term retrospective study that included the safety analysis of patients receiving allogeneic (immune system-incompatible) MSCs infusions to patients with autoimmune disease. In the study, the safety profiles of autoimmune patients receiving allogeneic MSCs infusion were evaluated. These infusions involve the use of donor-derived SCs, which have the potential to modulate immune system responses and suppress autoimmune responses. In this study, long-term follow-up and safety data of patients who received allogeneic SC infusion are presented. The results show that allogeneic stem cell infusion is generally safe in patients with autoimmune disease. Except for mild adverse events (eg, fever, mild headache) in some patients studied in the study, most patients did not report any serious adverse events, and their quality of life was generally improved after the infusion. In conclusion, researchers emphasize that allogeneic SC infusion is a potential option in the treatment of autoimmune diseases and can be applied safely.

Another type of SC that has shown promise in treating autoimmune diseases is HSC. Hematopoietic stem cells can be isolated from bone marrow and peripheral blood and have the ability to differentiate into various blood cell types.[51] One of the significant studies on HSCs was done by Darlington et al.[52] The study investigates the role of NK cells in regulating Th17 cells in patients undergoing autologous HSC transplantation (AHCHN) for relapsing-remissive multiple sclerosis (RRMS). Relapsing-remissive MS is a neurological disease with an autoimmune effect on the central nervous system. In the study, the immune responses of the patients were examined to evaluate the regulatory effect of NK cells on Th17 cells in patients who underwent AHCHN. Autologous HSC transplantation is a treatment method that involves collecting the patient's own SCs and then suppressing the immune system with high-dose chemotherapy. In the study, it is stated that NK cells interact directly to regulate Th17 cells, and this has an important role in the immune response after autogenous AHSCT. Natural killer cells have been shown to suppress the activation of Th17 cells, which helps reduce inflammation and control disease activity in RRMS patients.

While the use of SCs in treating autoimmune diseases is still in the early stages, early studies have shown that SCs have the potential to improve symptoms, reduce inflammation, and regulate the immune system's response. As research in this field continues, it is hoped that SC therapies will become an effective and safe treatment option for patients with autoimmune diseases.[53]

Recent Breakthroughs and Clinical Trials

Mesenchymal stem cells are seen as a promising approach in the treatment of autoimmune diseases since they have several properties that can be effective in preventing overreactions of the immune system. Mesenchymal stem cells can secrete biological molecules such as cytokines that can reduce inflammation and regulate the activity of immune system cells. In addition, MSCs can reduce tissue damage caused by autoimmune diseases by acting as an immunosuppressive effect against immune SCs.[54] Different types of SCs are used in the treatment of autoimmune diseases, including ESCs, ASCs, and iPSCs.

Embryonic stem cells are versatile cells that can differentiate into various types of cells. Due to these properties, they can be transformed into different cell types that can be used in the treatment of autoimmune diseases. However, the use of ESCs is controversial due to ethical concerns and immune response. Adult stem cells can be obtained from different tissues found in adults. For example, BMSCs, blood SCs, adipose tissue SCs, and nerve tissue SCs are seen as potential resources that can be used in the treatment of autoimmune diseases.[55]

Pluripotent stem cells, on the other hand, are versatile cells that can differentiate into various types of cells, similar to ESCs. However, the acquisition and use of these cells is less controversial. Man-made PSCs (for example, iPSCs) and PSCs from animals are seen as potential resources for the treatment of autoimmune diseases. For instance, in the study conducted by Wang et al.[56] 40 patients with SLE were observed. Mesenchymal stem cells obtained from the umbilical cord were administered to these patients in cases that did not respond to first-line therapy and/or increased disease activity. During the follow-up, the patients' SLE activity, drug use, and laboratory parameters (especially leukocyte, platelet, and CRP levels) were monitored. The results show that MSC treatment is safe and effective. A significant decrease in the SLE activity of the patients was observed, and more than half of the patients reduced or completely discontinued their drug use. In addition, the long-term effects of treatment appear to be positive. Another study conducted regarding SLE by Li et al.[57] aims to provide up-to-date information on MSC therapy in the treatment of lupus nephritis. Lupus nephritis is a common complication

in patients with SLE and in some cases can lead to kidney failure. MSC treatment is seen as a potential treatment option since it has anti-inflammatory and immunomodulatory properties that may be effective against the inflammatory process of the disease. The results show that MSC treatment causes a significant reduction in proteinuria and serum creatinine levels in lupus nephritis patients. In addition, an increase in the glomerular filtration rate (GFR) of patients was also observed after treatment. However, as stated in the study, there are still uncertainties regarding the optimal dose of MSC therapy, duration of treatment, and injection route. Apart from MSCs, other SC sources are also seen as remarkable agents in the treatment of lupus. For example, in the research of Huang et al.[58] 22 patients, all of whom received HSC mobilization, were involved to study. The patients had varying durations of lupus nephritis, with a median duration of 46 months. The majority of patients were female (13) and the rest were male (9). On average, each patient was given 7.3±3.8 million CD34+ cells per kg of body weight. All patients successfully underwent SC transplantation, with granulocyte and platelet engraftment taking an average of eight and nine days, respectively. The most common complications observed after HSC transplantation were fever and gastrointestinal symptoms. One patient (5%) died due to treatment-related issues. After a mean follow-up period of 72 months, 18 patients (82%) achieved complete remission, one patient (5%) achieved partial remission, and one patient required peritoneal dialysis 12 months after transplantation. The 5-year overall survival and disease-free survival rates were 91% and 53%, respectively. Of the six patients who relapsed, the recurrence rate was 27%. Autologous HSCs can be considered an alternative treatment option as they are safe and indicate positive results in patients who develop resistant lupus nephritis.

Besides SCs, it has been suggested recently that SC exosomes have promising potential in the treatment of autoimmune diseases. Stem cell exosomes are extracellular vesicles (EVs) and play an important role in intercellular communication. They contain a number of biological components such as active substances at the cellular level, proteins, nucleic acids, and lipids.[59] In addition, they have immunomodulatory effects in autoimmune diseases and can reduce inflammation and oxidative stress, which are important in the pathogenesis of these diseases. Therefore, SC exosomes are considered an alternative option in the treatment of autoimmune diseases. Many studies have shown that SC exosomes are a potential therapeutic tool in the treatment of autoimmune diseases. For example, in a study by Zheng et al.[60] it is suggested that exosomes secreted by bone marrow-derived mesenchymal stem cells (BMSCs) help reduce inflammation in RA patients. Researchers state that miRNA-192-5p, found in exosomes of MSCs, helps suppress inflammation. The study demonstrated *in vitro* and *in vivo* experiments that miRNA-192-5p of MSC exosomes suppressed inflammation and inhibited the proliferation of synovial cells. In addition, although they do not directly target the disease, stem cell-derived exosomes or SC treatments are examined to eliminate the effects they cause. In the study of Kuo et al.[61] the effect of BMSCs in the healing of diabetic wounds was investigated. In streptozotocin-induced diabetic rats, BMSC was injected into the wounds, and the wound-healing process was followed. The results showed faster wound healing in rats receiving BMSC treatment compared to the control group. This effect is thought to occur through BMSCs promoting tissue regeneration at the wound site, reducing new vessel formation and inflammation. Therefore, it shows that it can be used in diabetic wound healing as a potential treatment option.

Although the pathogenesis of MS is complex, it has been the subject of research recently with the use of various SCs. The study by Riordan et al.[62] investigated the clinical feasibility of using umbilical cord tissue-derived mesenchymal stem cells (UC-MSCs) in the MS. The researchers conducted a phase I/II clinical trial involving 20 patients with MS who received one intravenous infusion of UC-MSCs. The study evaluated the safety, tolerability, and potential efficacy of this treatment approach. The results showed that UC-MSCs were well-tolerated and safe, with no adverse events reported during the 13-month follow-up period. In addition, the study showed some evidence of potential efficacy in terms of clinical improvement, as measured by the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) score. The researchers noted that the study had several limitations, including a small sample size, lack of a placebo group, and a short follow-up period, which warrant further investigation.

Graves' disease is also an autoimmune disease, which, like MS, has a complex pathogenesis and can cause different diseases with its symptoms. The study by Park et al.[63] investigated the potential therapeutic effects of human placenta-derived mesenchymal stem cells (hPMSCs) on Graves' ophthalmopathy (GO) in female mice models. Graves' ophthalmopathy is an

autoimmune disorder that affects the eye muscles and can result in eye bulging, double vision, and eye irritation. In the study, hPMSCs were injected into the orbits of female mice with GO, and the effects on orbital adipogenesis (the formation of fat tissue in the eye) were evaluated. The results showed that hPMSCs significantly reduced orbital adipogenesis, as measured by both histological and molecular analyses. The researchers also found that hPMSCs reduced the expression of genes involved in adipocyte differentiation and lipid metabolism.

Numerous ongoing studies are investigating the use of SCs for autoimmune diseases, and these studies may involve different types of SCs. However, it is important to first determine the most appropriate source and target for SC therapy for a given disease before conducting studies.[64]

In conclusion, autoimmune diseases are a collective group of illnesses resulting from the immune system erroneously attacking its own cells or tissues in the body. Traditional treatments aim to alleviate symptoms, but their long-term effects may be limited, and achieving permanent remission can prove challenging for patients. Recently, innovative approaches, such as SCs therapy, have demonstrated potentially encouraging results in treating autoimmune diseases. Stem cells possess immunomodulatory and immunoregulatory properties, making them suitable for use in the treatment of autoimmune diseases. Stem cell therapy is emerging as a potentially efficacious treatment method, able to slow disease progression, reduce symptoms, and potentially achieve remission. Nonetheless, research in this field remains inadequately developed, necessitating further inquiry. Additionally, more data regarding the safety and effectiveness of SCs therapy must be gathered. Nevertheless, SCs therapy is viewed as a promising treatment approach for the future of autoimmune disease treatment.

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