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Research Article

Natural role of stem cells and their Potential for Tissue Regeneration and as Disease Treatment in the aging Population

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Abstract

Stem Cells play a crucial role in building and continuously repairing the human body. This review will explore the natural role of stem cells in the maintenance of the body, and their potential for tissue regeneration and disease treatment, particularly in the aging population and for those with orphan disease. In this paper, we review the various types of stem cells, their characteristics, and their capacity for expansion and their repair actions throughout the body. We also examine the role of exosomes in intracellular communication and their potential therapeutic applications. Furthermore, we investigate the impact of stem cells and exosomes on specific body systems, including bones, cartilage, muscles, brain and nervous systems, heart and vascular system, eyes, hair and skin, liver, lung, pancreas and sexual organs. The potential of stem cell therapy in addressing age related decline and various diseases is also highlighted throughout the review.

Keywords: Stem cells, Exosomes, Regeneration, Aging, Therapy, Differentiation, Tissue Repair, Immunomodulation, Vesicles, Growth factors, Cytokines, microRNAs

Glossary

1. Stem Cells: Undifferentiated cells capable of self-renewal and differentiation into various cell types.
2. Exosomes: Tiny extracellular vesicles involved in intercellular communication.
3. Multipotent: Stem cells capable of differentiating into multiple, but limited, cell types.
4. Pluripotent: Stem cells capable of differentiating into any cell type in the body.
5. Totipotent: Stem cells capable of forming all cell types, including embryonic and extraembryonic tissues.
6. Unipotent: Stem cells capable of differentiating into only one cell type.

Key Terms

1. Tissue regeneration
2. Disease treatment
3. Aging population
4. Orphan disease
5. Intracellular communication

6. Therapeutic applications
7. Age-related decline
8. Rejuvenation treatment
9. Immunomodulatory characteristics
10. Extracellular vesicles
11. Biomolecules
12. Regenerative medicine

Abbreviations

1. UC-MSCs: Umbilical Cord-derived Mesenchymal Stem Cells
2. HSCs: Hematopoietic Stem Cells
3. MSCs: Mesenchymal Stem Cells
4. CVDs: Cardiovascular Diseases
5. COPD: Chronic Obstructive Pulmonary Disease
6. IDF: International Diabetes Federation

Introduction

Stem cells are the building blocks of all multicellular organisms, with unique characteristics that enable them to divide into self-renewing cells; they also have the capacity to differentiate into various cell types. (i.e. neural, cardiac, hepatic, pancreatic (insulin secreting beta cells), bone, immune cells, and many others). As we age, there's a decrease in the number of stem cells, especially those with healthy proliferative ability.

Stem cells are programmed to secrete growth factors, and they are rich in cytokines, chemokines, micro-RNAs and exosomes, basically functioning as pharmacy to maintain tissue homeostasis, which promotes cell communication as well as regeneration and repair of specific tissues.

There are different types of stem cells depending on their characteristics and their capacity for expansion: Multipotent, Pluripotent, Progenitor, Totipotent and Unipotent.

Currently, clinical applications of stem cells in rejuvenation treatment are best done using human umbilical cord derived stem cells, since these cells are multipotent and can become more than one type of specialized cell e.g., umbilical cord, bone marrow, and Hematopoietic Stem Cells (HSCs). Given their ability to adapt to the areas where they are most needed, stem cells provide a very efficient way of aiding the body to heal itself. There are also a lot of studies that suggest that there are many additional opportunities for therapeutic uses for stem cells, particularly UC-MSCs given their low immunogenicity as well as their potent immunomodulatory characteristics [1, 2, 3, 4, 5, 6, 7, 8].

Exosomes

Exosomes are tiny extracellular vesicles produced by multivesicular bodies and released outside the cell, containing a double-membrane vesicle structure, and play a crucial role in intercellular communication under normal physiological and pathological conditions. These vesicles are naturally produced by the cells and can be found in various bodily fluids, including blood, saliva, and urine.

Exosomes have a diameter ranging from 40 to 150 nm and contain a variety of biomolecules such as proteins and nucleic acids. Exosomes transfer cellular cargoes to recipient cells, influencing immune responses, tissue repair, stem cell maintenance, and support the body in processes related to cardiovascular diseases, neurodegeneration, cancer, and inflammation. The study of exosomes is rapidly evolving with exciting potential for improving human health. Additionally, exosomes have low toxicity, low immunogenicity, and the ability to encapsulate a wide variety of substances, making them attractive drug delivery vehicles. Furthermore, mesenchymal stem cells (MSCs) secrete large amounts of exosomes, which have regenerative and tissue repair functions comparable to MSCs.

These exosomes offer advantages over MSC transplantation, as they can circumvent risks related to immune rejection and infection. Overall, exosomes hold significant potential for both diagnostic and therapeutic purposes [9, 10, 11, 12].

Endogenous stem cells and their Exosomes

Stem cells naturally occur in various tissues and organs throughout the body. They are undifferentiated cells that have the potential to develop into different cell types, playing a crucial role in the body's repair and regeneration processes. Stem cells are activated in response to injury or disease, where they divide and differentiate to replace damaged cells and tissues. This natural repair system is vital for maintaining healthy tissues and organs throughout life. Alongside stem cells, exosomes-tiny vesicles released by these cells-are emerging as critical players in cell to-cell communication, significantly impacting tissue repair and regeneration. These tiny vesicles play a crucial role in cell-to-cell communication, carrying essential proteins and genetic material to support various tissues and organs. As we age, we produce less stem cells and therefore less exosomes to help our body remain healthy and strong. Recent stud-

ies suggest that by introducing exosomes into our system, we can potentially boost the body's ability to heal and rejuvenate [13, 14]

By harnessing the power of exosomes, we may be able to enhance our overall well-being and promote longevity. Embracing the potential of exosome therapy could pave the way for a new frontier in regenerative medicine, offering a promising avenue for supporting general health and optimizing our body's natural healing processes [13,14, 15, 16].

Bones, Cartilage and Muscles

Osteoblasts are the essential cells responsible for bone formation and mineralization. Along with their exosomes, they play a critical role in the strengthening and restoration of bones, aiding in the healing process of damaged bones due to disease or trauma. Stem cell-derived exosomes have shown great potential in promoting osteoblast function and enhancing bone regeneration [18, 19].

Muscle stem cells and derived exosomes are key players in the healing and repair of muscle fibers. They contain various growth factors and signaling molecules that promote the regeneration of damaged muscles, leading to a stronger and healthier body [20].

Chondrocytes are the cells responsible for the formation, maintenance, and degradation of cartilage. These cells secrete an extracellular matrix that sustains cartilage health, helping the body repair joint tissues and cartilage damage [18].

Tendons and Ligaments play a crucial role in supporting the body's structure and movement. Tenocytes and fibroblasts work together to maintain the integrity and strength of these tissues. Specialized exosomes derived from these cells play a pivotal role in the repair and regeneration of damaged tendons and ligaments, contributing to improved flexibility and functionality. Recent research has highlighted the potential of stem cell-derived exosomes in enhancing the repair processes of tendons and ligaments, making them a promising therapeutic approach [19].

Brain and Nervous System

Neural diseases are a group of disorders that affect the nervous system, including the brain, spinal cord, and nerves. These diseases can cause a wide range of symptoms, including memory loss, muscle weakness, and difficulty speaking. Examples of neural diseases include Alzheimer's disease, Parkinson's disease, and multiple sclerosis, which affects up to 1 billion people worldwide. The combination of neural exosomes and dopamine secreting neurons is essential for the proper function of the nervous system. Neural exosomes are tiny vesicles that contain various growth factors and signaling molecules essential for the growth, repair, and maintenance of neurons. These exosomes are produced by various types of cells in the nervous system, including neurons and Glial cells, and are released into the extracellular matrix. Neural stem cell-derived exosomes are being investigated for their potential in regenerative therapies, particularly for traumatic brain injuries and neurodegenerative disease with very promising results [15, 21].

Dopamine Secreting Neurons

Dopamine-secreting neurons are a specific type of neuron that produces and releases dopamine, a neurotransmitter that plays a crucial role in the brain's reward and pleasure centers. Dopamine-secreting neurons are primarily found in the midbrain, but they also exist in other regions of the brain. Any damage or injury to the nervous system requires a balance between these two components to promote proper healing and recovery. Without both neural exosomes and dopamine-secreting neurons, the body's ability to repair its neural system would be compromised, leading to impaired brain function and potentially severe neurological disorders [22, 23, 24].

Neural diseases are a group of disorders that affect the nervous system, including the brain, spinal cord, and nerves. These diseases can cause a wide range of symptoms, including memory loss, muscle weakness, and difficulty speaking. Examples of neural diseases include Alzheimer's disease, Parkinson's disease, and multiple sclerosis. According to the World Health Organization (WHO), neurological disorders affect up to 1 billion people worldwide [25]. Recent studies have shown promising results in using stem cells to treat these conditions [26].

Researchers have successfully implanted lab-made dopamine-producing neurons into the brains of Parkinson's disease patients, which appear to reduce symptoms and improve quality of life [27].

Heart and Vascular System

The heart and vascular system are crucial for maintaining blood circulation throughout the body. Natural production of exosomes in the body diminishes over time, reducing the natural regeneration ability of these systems. Recent studies have shown that stem cell-derived exosomes can promote regeneration in both the heart and vascular system by containing proteins and genetic materials that stimulate the growth of new heart cells and blood vessels, leading to improved cardiac function and vascular health. According to the World Heart Federation's World Heart Report 2023, more than half a billion people around the world are affected by cardiovascular diseases (CVDs), which accounted for 20.5 million deaths in 2021-close to a third of all deaths globally [28, 29, 30].

One study from the Mayo Clinic discovered that stem cells could repair damage from heart attacks by restoring cardiac muscle to its pre-damage state, providing a blueprint for how stem cells may work across various conditions. Another study by UCLA researchers developed an experimental therapy using stem cells to prevent heart failure after heart attacks by enhancing tissue repair [31, 32, 33].

These advances highlight the potential of stem cells in promoting faster recovery and better outcomes for patients with heart and vascular conditions [34-43].

Hair and Skin

Hair

Hair dermal papilla cells play a critical role in the regulation of hair follicle growth, formation, and cycling. These cells are located at the base of the hair follicle and interact with the surrounding

epidermal cells to regulate hair growth. As we age, the function of these cells may decline, leading to hair loss or thinning. Recent stem cell research has shown that stem cell-derived exosomes can rejuvenate dermal papilla cells, promoting hair follicle regeneration and mitigating hair loss [34, 35, 36].

Skin

Epidermal exosomes contain various growth factors and signaling molecules that stimulate the proliferation and differentiation of skin cells, leading to improved skin health, appearance, and elasticity. Stem cell-derived exosomes have been shown to enhance these effects, supporting skin rejuvenation and healing. In addition to their potential benefits for hair growth and skin health, exosomes may also have therapeutic applications in wound healing and tissue regeneration. By delivering growth factors and other signaling molecules directly to damaged or diseased tissue, exosomes can promote healing and regeneration, potentially reducing the need for more invasive medical interventions [37, 38, 39, 40].

Liver and Kidney

The liver and kidneys are essential for maintaining overall health functioning as the body's primary filtration system to ensure blood quality. From the onset of blood circulation, the liver is exposed to numerous toxins. Exosomes play a pivotal role in preserving the health and functionality of the liver. However, as we age, the availability of exosomes diminishes, impairing the liver's ability to repair itself. Liver exosomes are small, membrane-bound vesicles that are released by cells of the liver. These exosomes contain various bio molecules such as proteins, lipids, and nucleic acids that are involved in cell-to-cell communication and signaling.

The kidneys clean the blood incredibly efficiently. When the kidneys get older or damaged, their ability to clean the blood decreases, causing the buildup of waste and excess fluids in the body. This can lead to serious health issues such as kidney disease, kidney failure, and even death. Without the filtration abilities of the liver and the kidneys, the quality of life diminishes rapidly. Once these organs have damaged, it is crucial to provide them with the right tools to stop or even reverse the deterioration which can have severe consequences. Recent studies show MSC-derived exosomes can regenerate liver and kidney tissues by alleviating liver fibrosis, enhancing tissue repair, and reducing inflammation [41, 42, 43, 44].

Lung

The lungs supply oxygen to the body via a complex network of blood vessels. When exposed to airborne toxins, they work to eliminate these toxins while continuing oxygenation. Exosomes play a crucial role in helping the lungs cope with these challenges. However, aging and ongoing exposure to environmental pollutants weaken the lungs' regenerative capacity, leading to diseases such as asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis, which cause symptoms like shortness of breath, coughing, and chest pain. Research shows that mesenchymal stem cell (MSC) therapy and specialized exosomes have anti-inflammatory effects, aiding lung function and capacity. Exosomes contain bioactive molecules, including proteins, lipids, and RNA that modulate immune responses and promote tissue repair. Recent studies highlight their potential in repairing lung tissue by regenerating alveolar cells, reducing fibrosis, and lessening chronic inflammation. This offers hope for better management of chronic lung conditions and improved quality of life [45, 46].

Pancreas

The pancreas has two main roles in the body. plays a key role in the digestive system by producing enzymes that break down food and hormones like insulin and glucagon that regulate blood sugar levels. When the pancreas isn't functioning properly, it can lead to serious health problems such as diabetes and pancreatitis.

Pancreatic diseases, which include diabetes, pancreatitis, cystic fibrosis, and exocrine pancreatic insufficiency, cause a wide range of symptoms, including abdominal pain, nausea, and vomiting. According to the International Diabetes Federation (IDF), approximately 10% of all people aged 20-79 worldwide - 537 million people-were living with diabetes as of 2021. This number is expected to rise to 643 million by 2030 and 783 million by 2045. Recent studies show promising advances in stem cell research for treating these conditions. Researchers have successfully produced fully functional pancreatic beta cells from stem cells, which could potentially replace damaged cells in diabetic patients. Additionally, a groundbreaking study demonstrated that stem cell transplants can reverse diabetes, offering hope for a potential cure [47, 48, 49, 50, 51, 52, 53].

Sexual Rejuvenation

As we age, the ability of our bodies to maintain blood flow, skin elasticity and muscle tone diminishes, resulting in many physical problems related to sexual health. Exosomes that normally would maintain the youthful health of sexual health is important for mental health as well as for physical wellbeing. During sex, the brain releases dopamine, serotonin, and oxytocin which are all neurotransmitters that boost feelings of happiness and relaxation, while also cutting stress hormone levels. This natural influx of chemicals can temporarily improve feelings of depression. Safer sex benefits go beyond the physical - healthier sex practices can positively impact your emotions, too. They support your emotional health by making sexual experiences even more enjoyable and stress-free.

As we age, the cells in the organs become scarce, and the body cannot naturally continue repairing them as before, resulting in issues like vaginal dryness, erectile disfunction, and incontinence, among others. Exosomes designed for the penile tissue that contains growth factors, have been shown to promote healing, increase blood flow, which can enhance performance, quality of erections and recovery time, increase length and girth (results vary from ¼ inch to 1 inch) and help reduce or eliminate incontinence. When applied to vaginal walls, the results have proven to rejuvenate and increase blood flow, which can restore lubrication, intensity and increase frequency of orgasms and improve sexual pleasure, restore vaginal size to what it was before age and other factors and help reduce or eliminate incontinence [54, 55, 56].

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