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The development and application of stem cells in biomedicine

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Abstract. Over the past few decades, significant advancements have been made in the field of stem cell research. Through the utilization of a literature review methodology, our study delved into an examination of three fundamental sources of stem cells, their respective activities, and the possible therapeutic applications of stem cells within the field of regenerative medicine. Furthermore, the discourse around ethical concerns pertaining to stem cell research is examined, while existing literature is consulted to identify the regulatory frameworks governing the lawful execution of embryonic stem cell research. The investigation of stem cells in the field of regenerative medicine holds significant potential for advancing human welfare. Stem cells have the capacity to replace outmoded therapy modalities, thereby offering improved alternatives. Furthermore, several diseases that were previously deemed incurable have now become viable candidates for treatment through the application of stem cell research. This research on stem cells has a dual purpose: advancing the field of regenerative medicine and deepening our understanding of life, enabling us to witness the successive wonders of existence.

Keywords: stem cells, biomedicine, ethical issues

1. Introduction

Since the seminal discovery made by Japanese scientist Yamanaka in 2006, it has been established that somatic cells possess the capability to be reprogrammed into induced pluripotent stem cells (iPSCs), which exhibit similar characteristics to embryonic stem cells. This reprogramming process is achieved through the introduction of four specific transcription factors, namely Oct4, Sox2, Klf4, and c-Myc. Consequently, the investigation of stem cells has emerged as a prominent area of interest within the field of regenerative medicine. Numerous researchers have been engaged in the investigation of stem cells. Numerous hospitals have also emerged as providers of stem cell therapy for patients. There are now around 1066 ongoing studies investigating the potential therapeutic applications of stem cells. The field of stem cell research has witnessed significant advancements, with an increasing number of fundamental studies being successfully conducted. Simultaneously, an increasing number of previously incurable illnesses have been discovered to be amenable to treatment through diverse stem cell therapies. Embryonic stem cells are a type of pluripotent cells that has the ability to undergo self-replication. The cells in question exhibit an undifferentiated state and have the capacity to undergo differentiation into diverse cell types, tissues, and potentially even organs. Stem cells can be classified into two main categories, namely embryonic stem cells and adult stem cells, based on their developmental stage. Stem cells, possessing the capacity for self-renewal, assume a crucial function in the process of organ

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restoration and tissue rejuvenation. The investigation of stem cells possesses the capacity to fundamentally transform the field of medical technology.

This study provides a comprehensive analysis of the progression and utilization of stem cells in the field of biomedicine. It achieves this by succinctly outlining the fundamental principles, functionalities, and applications of stem cells.

2. Basic knowledge of stem cells

2.1. Embryonic Stem cells

Embryonic stem cells (ESCs) are a type of stem cell found in the initial stages of mammalian embryonic development, specifically in blastocysts and the genital ridge during early embryogenesis. The existing embryonic stem cell lines predominantly originate from the inner cell mass found within the blastocyst. ESCs are a category of pluripotent stem cells that are obtained from early-stage embryos. When embryonic stem (ES) cells are exposed to differentiation inhibitors and experience alterations in their culture circumstances, they undergo a process where they aggregate to form structures known as embryoid bodies. These embryoid bodies subsequently undergo differentiation into various cell types, which is influenced by distinct induction and culture methods.

Embryonic stem cells possess the capacity to undergo differentiation into several cell types, including hematopoietic cells, vascular endothelial cells, neuronal cells, cardiac cells, muscle cells, fat cells, and ointment cells. In vitro, the differentiation of embryonic stem cells into hematopoietic stem cells can be induced by utilizing bone marrow stromal cells and their corresponding culture media. In a similar vein, embryonic stem cells possess the ability to undergo differentiation into diverse cell types when subjected to varying environmental cues. In contrast to the differentiation processes observed in other cell types, the circumstances required for the differentiation of ES cells into dermal cells are notably rigorous, resulting in a relatively low success rate.

The utilization and advantages of embryonic stem cells in the field of medical research encompass several areas. Firstly, the examination of pharmacological impacts and toxicity of diverse cells can be facilitated through the utilization of cells derived from embryonic stem cells or cultured tissues. This approach has the potential to replace a significant portion of animal experiments and clinical investigations [1]. Additionally, employing the patient's own embryonic stem cells for tissue culture and subsequently transplanting the organs developed from these cells back into the patient can circumvent issues of rejection. In many instances, this intervention can lead to enduring treatment outcomes following a single intervention [1].

Embryonic stem cells possess unparalleled potential for advancements in medical research and therapeutic applications; nonetheless, their utilization also engenders ethical quandaries. The primary focus of bioethical discourse is around the extraction of embryonic stem cells, which results in the destruction of the embryo. Consequently, the question of whether the embryo should be considered a form of life has emerged as a significant concern. This issue extends beyond the examination of whether embryonic stem cells do harm to life or pose a threat to human existence. In relation to this matter, certain nations concur that the examination of embryos at the age of 14 days is permissible, as they have not yet initiated the process of development and differentiation into distinct tissues and organs [2].

2.2. Adult stem cells

The term "adult stem cells" pertains to pluripotent stem cells that are present in many tissues inside the human body. These organisms possess the capacity for autonomous regeneration, preservation of bodily homeostasis, and initiation of cellular rejuvenation and tissue restoration. The nomenclature of adult stem cells is based on their source and the specific tissue cells they differentiate into. Examples include hematopoietic stem cells, neural stem cells, and bone marrow mesenchymal stem cells, among others. When considering medical research and cultivation, adult stem cells, particularly bone marrow mesenchymal stem cells, offer advantages over embryonic stem cells due to their ethical acceptability and ease of collection. In vitro expansion of these cells may be achieved on a massive scale, showcasing

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their remarkable adaptability and potential for generating a substantial supply of biomaterials in the field of regenerative medicine.

In vitro cultivation and in vivo stimulation define adult stem cell flexibility. Adult stem cells can differentiate into multiple cell types in response to environmental signals. In a wearable culture system, these cells may preserve their potential to develop into multiple cell lineages. Adult stem cells can differentiate into skeletal muscle, cardiomyocyte, skin, and nerve cells. However, adult stem cells have limitations. The body has few adult stem cells, making separation and purification difficult. As they age, their population declines. Adult stem cell differentiation's limitations limit its clinical use.

Adult stem cells are used in cell transplantation therapy to differentiate into new tissues and reintegrate with the surrounding tissues. Adult stem cells also secrete paracrine proteins that boost cell regeneration in lesions and wounds, reducing scarring. Neural and bone marrow mesenchymal stem cells can differentiate, but many undifferentiated cells remain. Human adult stem cells can be isolated and grown using current technologies. Some cells from the patient's skin tissue, including the foreskin, can be cultured into fibers and epidermal cells using this enhanced procedure. This method allows ex vivo stem cell development as skin regeneration biomaterials.

2.3. Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) are obtained from somatic cells and exhibit the ability to develop into many cell lineages while maintaining pluripotency and sustained proliferation. In the year 2006, the research team led by Shinya Yamanaka accomplished the successful induction of iPSCs in mouse embryos and skin fibroblasts. This was achieved by employing a viral vector that carried a combination of four transcription factors (Oct4, Sox2, Klf4, and c-Myc). Consequently, these cells underwent reprogramming, exhibiting characteristics similar to embryonic stem cells in various aspects such as morphology, gene expression, protein expression, proliferation, and differentiation capacity. In contrast to embryonic stem cells (ESCs), iPSCs present a number of benefits. iPSCs can be acquired through genetic manipulation, thereby circumventing ethical dilemmas associated with their source. Additionally, iPSCs can be employed in the creation of syngeneic control cell lines using gene editing techniques, enabling the modification of DNA for therapeutic purposes in the treatment of human diseases [3-4]. Nevertheless, iPSCs do possess several limitations: The reprogramming process exhibits suboptimal efficiency, while the genetic editing procedure carries a potential danger of cancer as a result of gene replacement. Moreover, iPSCs demonstrate a tendency towards nuclear shape instability, which has the potential to undermine their genetic stability despite their rapid differentiation capabilities. However, iPSCs possess a wide array of applications that span from the transplantation of cells and the repair of organs to the modeling of diseases for research objectives, in addition to their use in drug screening processes. The challenge of effectively and safely utilizing iPSCs persists [5].

3. Working mechenism of stem cells

3.1. Self-renewal of stem cells

Stem cells possess notable attributes like their powerful potential for self-renewal and their ability to undergo differentiation into several cellular lineages. Stem cells sustain their self-renewal capacity through two distinct forms of division, namely symmetric and asymmetric division.

Neural stem cells, which have significant importance, also undergo both forms of division. Symmetric division leads to the generation of two neural stem cells (NSCs) or two neural progenitor cells (NPCs). Asymmetric division results in the generation of either one NSC and one NPC, or one NSC and one cell undergoing apoptosis. During the process of nervous system development, NSCs initially perform symmetric division, followed by asymmetric neurogenic division. In this latter division, one of the daughter cells retains its proliferative properties as a NPC, while the other daughter cell undergoes enlargement, subsequent division, and ultimately differentiation. After the completion of this process, NSCs can either undergo apoptosis or reach a senescent state characterized by decreased proliferation [6].

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The process of autophagy, which is a widespread cellular self-defense mechanism, entails the sequestration of proteins or organelles into vesicles that subsequently merge with lysosomes, resulting in the formation of autolysosomes where destruction occurs. The majority of stem cells in the human body exhibit a condition of quiescence and possess a lengthy lifespan. However, it is important to note that these cells have limited capabilities in terms of waste clearance during this dormant state. Consequently, they rely on autophagy to a greater extent compared to other types of cells [7].

3.2. Cases of stem cell therapy

The process of differentiating induced pluripotent stem cells (iPSCs) into cardiomyocytes with a directional orientation. iPSCs possess the inherent ability to undergo spontaneous differentiation into embryoid bodies (EBs), resulting in the emergence of contractile cardiomyocytes. Research has substantiated that the molecular composition and functional attributes of differentiated cardiomyocytes, specifically induced pluripotent stem cell-derived cardiomyocytes (iPSCs-CMs), bear resemblance to those of nascent cardiomyocytes. Furthermore, iPSCs-CMs possess the capacity for proliferation. The electrophysiological investigations provided confirmation that iPSCs-CMs displayed action potentials resembling those of ventricular, atrial, and sinoatrial node cells. Additionally, these cells showed ion channels characteristic of cardiomyocytes. iPSCs-CMs exhibited a high degree of sensitivity to neurohormonal stimuli. The addition of isoproterenol resulted in a notable rise in the frequency of action potentials. Conversely, the introduction of lidocaine, nifedipine, and E4031, which are blockers of sodium, L-type calcium, and potassium channels respectively, led to a considerable decrease in the frequency of action potentials. In light of the suboptimal efficacy observed in the differentiation of iPSCs, scientists have endeavored to enhance the effectiveness of cardiac differentiation by introducing cardiomyogenic proteins and transforming growth factor beta (TGF−β) released by endodermal cells. Research has indicated that the inclusion of activin A, bone morphogenetic protein 4/2, basic fibroblast growth factor, and Wnt inhibitor in the medium can significantly enhance the efficiency of cellular differentiation.

A group of researchers implanted undifferentiated iPSCs and fibroblasts into mice with acute myocardial infarction in 2009. Color Doppler echocardiography showed a statistically significant improvement in cardiac ejection fraction in the iPSC group compared to the control group. This difference was evident from week one to week four of the trial. In the iPSC group, the ventricular wall was mostly normal. The control group had a thinner anterior wall of the left ventricle and a tumor on the apex in the fourth week. The iPSC group had significantly lower left ventricular end-diastolic diameter (LVDd) and QT dispersion than the control group. The iPSCs group had a smaller heart volume than the control group after tissue biopsy. When implanted into immunodeficient animals with myocardial infarction, undifferentiated iPSCs were tumor-prone in the infarcted myocardium and surrounding areas. Immunocompetent mice did not develop tumors for 8 weeks. This shows that normal immune function can create a milieu for iPSC myocardial tissue development. In 2011, Mauritz et al. found that Flk-1+ cells from iPSCs could differentiate into cardiomyocytes in vitro and in vivo. Moreover, transplanting iPSCs-Flk1+ cells into animals with acute myocardial infarction improved cardiac function and reduced cardiac remodeling. This discovery was significant [8].

4. The potential of stem cells to treat cancer

The observation that mesenchymal stem cells (MSCs) exhibit a tropism towards tumor tissue has generated significant attention among researchers. In the year 1999, Maestroni and colleagues put up the proposition that MSCs possess the ability to relocate to tumor locations, thereby establishing this attribute as a distinctive homing trait of MSCs. Tumors are sometimes referred to as “incurable wounds”, and it has been extensively demonstrated via various research that MSCs exhibit tropism towards wound sites. MSCs has the capacity to engage with tumor cells via diverse mechanisms, hence exerting either promotive or inhibitory effects on tumor formation. According to Maestroni’s research, it was observed that MSCs produced from bone marrow have the ability to secrete various soluble factors that possess inhibitory properties against the proliferation of lung cancer and B16 melanoma in murine models. The

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confirmation of MSCs' tropism towards glioma was demonstrated by experimental studies conducted on rats. Furthermore, the selectivity of MSCs' tropism towards glioma was observed to be distinct when compared to human neural stem cells (hNSC). The acquisition and in vitro expansion of hNSC pose significant challenges, hence imposing limitations on its practical utilization. MSCs can be readily acquired, cultured, and expanded in vitro. As previously said, tumors can be likened to wounds, as they exhibit a constant release of cytokines and chemokines, thereby attracting a diverse array of cells, including MSCs. Numerous types of cancers, including pancreatic cancer, ovarian cancer, colorectal cancer, breast cancer, lung cancer, and malignant glioma, exhibit the characteristic of facilitating the homing of MSCs. The precise mechanism underlying the promotion of MSC migration by malignancies remains uncertain and could potentially be linked to the biological properties of the tumor microenvironment. MSC integration into tumor stroma is thought to be caused by increased inflammatory chemokines and growth factors. The tumor is often seen as a "wound," causing local inflammation. MSCs secrete various soluble factors, such as epidermal growth factor, vascular endothelial growth factor-a, fibroblast growth factor, platelet-derived growth factor, matrix derived growth factor-1A, interleukin-8, interleukin-6, granulocyte giant cell colony-stimulating factor, and transforming growth factor-β, due to chronic inflammation. With these components, MSC migration was successful. MSCs are ideal for transporting anticancer bioactive compounds. This is due to their propensity for tumors, ability to integrate into tumor cell stroma, and immunomodulatory properties. Adding anti-cancer genes to MSCs has been shown to work. In pancreatic cancer, interferon is transfected, interleukin-12 is in melanoma and liver cancer, interferon- is in leukemia, interleukin-2 is in glioblastoma, NK4 is in lung cancer, and TRAIL. MSC tropism targets oncolytic virus to tumors. Animal studies show that transplanting MSCs laden with oncolytic adenovirus to the tumor site eliminates tumors better than injecting it [9].

5. Ethical issues in stem cell research

One of the notable areas of interest within stem cell research is to the potential therapeutic applications of cloning individual organs. Undoubtedly, the most appealing approach in this regard involves employing the patient's own cells to clone cells, tissues, and organs. According to current scientific understanding, it is now postulated that the process of somatic cell nuclear transfer involves the fusion of the patient's somatic cells with enucleated egg cells obtained from a donor. Subsequently, the reactivation of the nucleus takes place, leading to the establishment of embryonic pluripotent stem cell lines. These cell lines are then subjected to in vitro cultivation and induced to undergo differentiation into various cell types, such as blood cells, pancreatic cells, nerve cells, and heart cells, among others. These cells has the potential to be employed in the treatment of various medical disorders, including but not limited to leukemia, diabetes [10], heart disease, Parkinson's disease, Alzheimer's disease, stroke, spinal cord injury, burn, and other fundamental ailments, with the aim of delivering cell-based therapeutic interventions. The potential utilization of human stem cells in the regeneration of intricate human tissues and organs may present novel opportunities in the field of organ transplantation. The prolonged administration of immunosuppressants in individuals undergoing allogeneic transplantation will heighten their susceptibility to infection and malignancy. One of the primary benefits of therapeutic cloning is in its ability to utilize stem cells and tissues derived from a clone of the patient's somatic cells. This technique guarantees that the cloned cells' DNA coding and gene phenotype match those of the patient, avoiding rejection and improving results for most patients. There is consensus that trauma, burns, and spinal cord injuries can be treated without human cloning or stem cell research. Therapeutic cloning can reduce or eliminate rejection in genetically linked diseases like leukemia, diabetes, and heart disease. Is its functioning sufficient to replace the original organ? This is how well the entity has all the necessary functions to do its role. How durable are these fast-engineered organs and tissues? Using stem cells, tissues, and organs from the patient's somatic cells ensures a full alignment between their DNA coding and gene phenotypes, ensuring genetic consistency. Newly cloned organs and tissues may inherit dangerous genes. Analogous illnesses will return if the human body's interior environment meets its needs for adaptability and survival. If any of the above queries fails to match the criteria, it may harm

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patients' well-being and ability to reach optimal health. Conversely, it may not lower patients' quality of life, forcing them to endure their condition again. Patients and researchers may benefit from unwanted results. However, utilitarianism or morality must be considered [2].

6. Conclusion

The medical research field recognizes the significant potential of stem cells due to their extraordinary capacity for continual proliferation and differentiation. This unique characteristic enables the generation or maintenance of multiple lives starting from the initial phases of embryonic development. The investigation of stem cells offers significant contributions to the fields of biology and medicine, facilitating a full comprehension of the fundamental aspects of life. Stem cell research has demonstrated significant advancements in fulfilling numerous aspirations and theoretical postulations, effectively bridging the divide between imaginative concepts and tangible outcomes.

Extensive research has been conducted on the potential benefits of stem cells; yet, it is imperative to acknowledge the presence of uncontrollable or accepted negative effects associated with their utilization. It is imperative to acknowledge the incomplete examination of the drawbacks associated with employing stem cells as medicinal resources, while we persist in our pursuit of advancing stem cell technology for regenerative medicine in forthcoming endeavors.

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