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Stem cell therapy: A new concept of medical application in Pharmacology

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Abstract:

Stem-cell therapy is an intervention strategy that introduces new adult stem cells into damaged tissue in order to treat disease or injury. Many medical researchers believe that stem-cell treatments have the potential to change the face of human disease and alleviate suffering. The ability of stem cells to self-renew and give rise to subsequent generations with variable degrees of differentiation capacities, offers significant potential for generation of tissues that can potentially replace diseased and damaged areas in the body, with minimal risk of rejection and side effects. The general objectives in the area of stem cell research in the next few years, are related to identification of therapeutic targets and potential therapeutic tests, studies of cell differentiation and physiological mechanisms, culture conditions of pluripotent stem cells and efficacy and safety tests for stem cell-based drugs or procedures to be performed in both animal and human models in the corresponding clinical trials.

Key Words: Stem Cell, Gene therapy, Biomaterial, Pharmacology

Introduction

A great interest has arisen in research in the field of stem cells, which may have important applications in tissue engineering, regenerative medicine, cell therapy, and gene therapy because of their great therapeutic potential, which may have important applications. Cell therapy is based on transplantation of live cells into an organism in order to repair a tissue or restore lost or defective functions [1].Cells mainly used for such advanced therapies are stem cells, because of their ability to differentiate into the specific cells required for repairing damaged or defective tissues or cells.Regenerative medicine is in turn a multidisciplinary area aimed at maintenance, improvement, or restoration of cell, tissue, or organ function using methods mainly related to cell therapy, gene therapy, and tissue engineering. Tissue engineering is the use of cells, biological factors, and biomaterials, alone or in combination, with the goal of restoring normal tissue structure and function. The idea of tissue engineering arises from the problem that cell-based therapies rely on an intact scaffold of the diseased or injured tissue.[2,3]

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Stem cell therapy

For practical purposes, human embryonic stem cells are used in 13% of cell therapy procedures, while fetal stem cells are used in 2%, umbilical cord stem cells in 10%, and adult stem cells in 75% of treatments. To date, the most relevant therapeutic indications of cell therapy have been cardiovascular and ischemic diseases, diabetes, hematopoietic diseases, liver diseases and, more recently, orthopedics [60]. For example, more than 25,000 hematopoietic stem cell transplantations (HSCTs) are performed every year for the treatment of lymphoma, leukemia, immunodeficiency illnesses, congenital metabolic defects, hemoglobinopathies, and myelodysplastic and myeloproliferative syndromes [4]. Depending on the characteristics of the different therapeutic protocols and on the requirements of each condition, each type of stem cell has its advantages and disadvantages. Thus, embryonic stem cells have the advantages of being pluripotent, easy to isolate, and highly productive in culture, in addition to showing a high capacity to integrate into fetal tissue during development. By contrast, their disadvantages include immune rejection, the possibility that they differentiate into inadequate cell types or induce tumors, and contamination risks. Germ stem cells are also pluripotent, but the source from which they are harvested is scarce, and they may develop embryonic teratoma cells in vivo. Adult stem cells are multipotent, have a greater differentiation potential, less likely to induce no immune rejection reactions, and may be stimulated by drugs. Their disadvantages include that they are scarce and difficult to isolate, grow slowly, differentiate poorly in culture, and are difficult to handle and produce in adequate amounts for transplantation. In addition, they behave differently depending on the source tissue, show telomere shortening, and may carry the genetic abnormalities inherited or acquired by the donor[5,6.7] These disadvantages of adult stem cells are less marked in some of the above mentioned subtypes, such as mesenchymal stem cells obtained from bone marrow or adipose tissue, or iPSCs. In these cases, harvesting and production are characterized by their easiness and increased yield rates in the growth of the cultures. Their growth is slow but meets experimental requirements, and their differentiation and implantation are highly adequate [8,62,63].

Overall, at least three types of therapeutic strategies are considered when using stem cells. The first is stimulation of endogenous stem cells using growth factors, cytokines, and second messengers, which are able to induce self-repair of damaged tissues or organs. The second alternative is direct administration of stem cells so that they differentiate at the damaged or non-

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functional tissue sites. The third possibility is transplantation of cells, tissues, or organs taken from cultures of stem cell-derived differentiated cells. [9,10]

The US Food and Drug Administration defines somatic cell therapy as the administration of autologous, allogeneic, or xenogeneic non-germ cells--excluding blood products for transfusion--which have been manipulated or processed and propagated, expanded, selected ex vivo, or drug-treated [11]. Cell therapy applications are related to the treatment of organ-specific diseases such as diabetes or liver diseases. Cell therapy for diabetes is based on islet transplantation into the portal vein of the liver and results in an improved glucose homeostasis, but graft function is gradually lost in a few years after transplantation. Liver diseases (congenital, acute, or chronic) may be treated by hepatocyte transplantation, a technique under development and with significant disadvantages derived from difficulties in hepatocyte culture and maintenance. The future here lies in implantation of hepatic stem cells, or in implantation of hepatic cells obtained by differentiation of a different type of stem cell, such as mesenchymal stem cells. [12,13]

Other applications, still in their first steps, include treatment of hereditary monogenic diseases such as hemophilia using hepatic sinusoidal endothelial cells [14] or murine iPSCs obtained by fibroblast differentiation into endothelial cells or their precursors [15]. As regards hemophilia, an optimum candidate because it is a monogenic disease and requires low to moderate expression levels of the deficient coagulation factor to achieve a moderate phenotype of disease, great progress is being made in both gene therapy and cell therapy using viral and non-viral vectors. The Liras et al. group has reported encouraging preliminary results using non-viral vectors and mesenchymal stem cells derived from adult human adipose tissue [16 17].Very recently, Fagoonee et al. [69] first showed that adult germ line cell-derived pluripotent stem cells (GPSCs) may differentiate into hepatocytes in vitro, which offers a great potential in cell therapy for a very wide variety of liver diseases.

Histocompatible stem cell therapy

Since one of the most important applications of cell therapy is replacement of the structure and function of damaged or diseased tissues and organs, avoidance or reduction of rejection due to a natural immune response of the host to the transplant is a highly relevant consideration. Recent progress in nuclear transference from human somatic cells, as well as the iPSC technology, have allowed for availability of lineages of all three germ layers genetically identical to those of the donor patient, which permits safe transplantation of organ-tissue-specific adult stem cells with no

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immune rejection [18]. On the other hand, adipose-derived mesenchymal stem cells (ASCs) are able to produce adipokines, including many interleukines [19]. ASCs also have immunosuppressive capacity, regulating inflammatory processes and T-cell immune response [20-21]. The lack of HLA-DR expression and immunosuppressive properties of ASCs make these cells highly valuable in allogeneic transplantation to prevent tissue rejection. They do not induce alloreactivity in vitro with incompatible lymphocytes and suppress the antigen response reaction by lymphocytes. These findings support the idea that ASCs share immunosuppressive properties with bone marrow-derived MSCs and may therefore represent a new alternative for conditions related to the immune system [22-23].

General aspects of stem cells

The main properties that characterize stem cells include their indefinite capacity to renew themselves and leave their initial undifferentiated state to become cells of several lineages. This is possible because they divide symmetrically and/or asymmetrically, i.e. each stem cell results in two daughter cells, one of which preserves its potential for differentiation and self-renewal, while the other cell directs itself toward a given cell lineage, or they both retain their initial characteristics.[24-25] Stem cells are able to renew themselves and produce mature cells with specific characteristics and functions by differentiating in response to certain physiological stimuli. Different types of stem cells are distinguished based on their potential and source. These include the so-called totipotent embryonic cells, which appear in the early stages of embryo development, before blastocyst formation, capable of forming a complete organism, as well as all intra and extra embryonic tissues. Multipotent adult cells (such as hematopoietic cells, which may differentiate into platelets, red blood cells, or white blood cells) are partially specialized cells but are able to form a specific number of cell types. Unipotent cells only differentiate into a single cell lineage, are found in the different body tissues, and their function is to act as cell reservoirs in the different tissues.[26] Germ stem cells are pluripotent embryonic stem cells derived from gonadal buds of the embryo which, after a normal embryonic development, will give rise to oocytes and spermatozoa.

In the fetal stage there are also stem cells with differentiation and self-renewal abilities. These stem cells occur in fetal tissues and organs such as blood, liver, and lung and have similar characteristics to their counterparts in adult tissues, although they show a greater capacity to

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expand and differentiate.Their origin could be in embryonic cells or in progenitors unrelated to embryonic stem cells.[27-28]

Types of stem cells therapy

Hematopoietic stem cells together with mesenchymal stem cells, the so-called "side population", and multipotent adult progenitor cells (MAPCs), are the stem cells forming bone marrow [29]. Their role is maintenance and turnover of blood cells and immune system.The high rate of regeneration of the liver, as compared to other tissues such as brain tissue, is due to proliferation of two types of liver cells, hepatocytes, and oval cells (stem cells). In response to acute liver injuries (hepatectomy or hepatotoxin exposure), hepatocytes regenerate damaged tissue, while oval cells are activated in pathological conditions where hepatocytes are not able to divide (acute alcohol poisoning, phenobarbital exposure, etc.), proliferating and converting into functional hepatocytes [30].

In skeletal muscle, the stem cells, called satellite cells, are in a latent state and are activated following muscle injury to proliferate and differentiate into muscle tissue. Muscle-derived stem cells have a greater ability for muscle regeneration [31]. In cardiac tissue, cardiac progenitor cells are multipotent and may differentiate both in vitro and in vivo into cardiomyocytes, smooth muscle cells, and vascular endothelial cells [36,37].

Neuronal stem cells able to replace damaged neurons have been reported in the nervous system of birds, reptiles, mammalians, and humans. They are located in the dentate fascia of hippocampus and the subventricular area of lateral ventricles [38,39]. Stem cells have also recently been found in the peripheral nerve system (in the carotid body) [40]. Astrocytes, which are glial cells, have been proposed as multipotent stem cells in human brain [41,32].

The high renewal capacity of the skin is due to the presence in the epidermis of stem cells acting as a cell reservoir. These include epidermal stem cells, mainly located in the protuberance of hair follicle and which are capable of self-renewal for long time periods and differentiation into specialized cells, and transient amplifying cells, distributed throughout basal lamina and showing in vivo a very high division rate, but having a lower differentiation capacity [42,33].

Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) from somatic cells are revolutionizing the field of stem cells. Obtained by reprogramming somatic stem cells of a patient through the introduction of certain transcription factors [43-48].The iPSC technology offers the possibility of developing

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patient-specific cell therapy protocols [49,35] because use of genetically identical cells may prevent immune rejection. In addition, unlike embryonic stem cells, iPSCs do not raise a bioethical debate, and are therefore a "consensus" alternative that does not require use of human oocytes or embryos . Moreover, iPSCs are not subject to special regulations and have shown a high molecular and functional similarity to embryonic cells [52,53].

Highly encouraging results have been achieved with iPSCs from skin fibroblasts, differentiated to insulin-secreting pancreatic islets [54]; in lateral amyotrophic sclerosion [55]; and in many other conditions such as adenosine deaminase deficiency combined with severe immunodeficiency, Shwachman-Bodian-Diamond syndrome, type III Gaucher disease, Duchenne and Becker muscular dystrophy, Parkinson and Huntington disease, diabetes mellitus, or Down syndrome [56]. Good results have also been reported in spinal muscular atrophy [57].

Suitability of infrastructure and technical staff

Any procedure related to cell therapy requires a strict control of manipulation and facilities. In addition, it should not be forgotten that cell therapy products are considered as drugs, and the same or a similar type of regulation should therefore be followed for them [50].Products must be carefully detailed and described, stating whether autologous, allogeneic, or xenogeneic cells are administered. Xenogeneic cells are included by the US Food and Drug Administration [78] It should also be detailed whether cells have been manipulated together with other non-cell materials such as synthetic or natural biomaterials, with other types of materials or agents such as growth factors or serum.

As regards the production process, a detailed description must be given of all procedures related to product quality in the Standard Operating Procedures (SOPs), as for conventional medical products. [52,53].The purity, safety, functionality, and identity criteria used for conventional drugs must be met.the production process must occur in a highly aseptic environment with comprehensive controls of both raw materials and handlers. Needless to say that production process should be highly reproducible and validated both on a small scale for a single patient and on a large scale. For an autologous therapy procedure, cell harvesting from the patient will be aimed at collecting healthy cells whenever this is possible, because in some cases, if no mosaicism exists and the disease is inherited, all cells will carry the relevant mutation, in which

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case this procedure will not be feasible. In hemophilia the situation may be favorable, because mosaicism is found in 30% of the cases [79,54].

Cell therapy products should adhere to the Current Good Manufacturing Practices, including quality control and quality assurance programs, which establish minimum quality requirements for management, staff, equipment, documentation, production, quality control, contracting-out, claims, product recall, and self-inspection. Production and distribution should be controlled by the relevant local or national authorities based on the International Conference on Harmonization of Pharmaceuticals for Human Use, which standardizes the potential interpretations and applications of the corresponding recommendations [80,55].

The most important rooms of these facilities include the so-called clean rooms, which are classified in four classes (A-D) depending on air purity, based on the number of particles of two sizes (≥ 0.5 μm, ≥ 5 μm).As regards to the number of technical staff, this should be the minimum required and should be especially trained in basic hygiene measures required for manipulation in a clean room. Material and staff flows should be separated and be unidirectional to minimize cross contamination, and control and documentation of all activities is necessary. Technical staff should have adequate qualification both for the conduct and surveillance of all activities.[56]Good Manufacturing Practice for Pharmaceutical Manufacturers is a general legal requirement for all biological medicinal products before their marketing or distribution. [84].

Biomaterials for Cellular Therapy

In advanced therapies, particularly in cell therapy and tissue engineering, the biomaterial supporting the biological product has a similar or even more important role as the product itself. Such biomaterials serve as the matrix for nesting of implanted cells and tissues because they mimic the functions of the tissue extracellular matrix.Biomaterials for cell therapy should be biocompatible to prevent immune rejection or necrosis.[57,58] They should also be biodegradable and assimilable without causing an inflammatory response, and should have certain structural and mechanical properties. Their primary role is to facilitate location and distribution of somatic cells into specific body sites--in much the same way as excipients in classical pharmacology--and to maintain the three-dimensional architecture that allows for formation and differentiation of new tissue.

Materials may be metals, ceramic materials, natural materials, and synthetic polymers, or combinations thereof. Synthetic polymers are biocompatible materials (although less so than

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natural materials) whose three-dimensional structure may easily and reproducibly be manufactured and shaped. Their degradation rate may be controlled, they are free from pathogens, and bioactive molecules may be incorporated into them.[59,60]Their disadvantage is that they may induce fibrous encapsulation. Natural polymers such as collagen, alginate, or keratin extracts are also biocompatible and, as synthetic polymers, may be incorporated active biomolecules. In any case, use of one or the other type of biomaterial is always related to the administration route in cell therapy protocols, implantation or injection. Thus, in the injection-based procedure, which is simpler and requires no surgery but can only be used for certain areas, biomaterials are usually in a hydrogel state, forming a hydrophilic polymer network, as occurs in PEO (polyethylene oxide), PVA (polyvinyl alcohol), PAA (polyacrylic acid), agarose, alginate, collagen, and hyaluronic acid [85,86,61].

Research on biomaterials for cell therapy is aimed not only at finding or synthesizing new materials, but also at designing methods that increase their efficacy.For example, control of the porous structure of these materials is very important for increasing their efficacy in tissue regeneration (through solvent casting/particulate leaching, freeze-drying, fiber bonding, electrospinning, melt molding, membrane lamination, or hydrocarbon templating). An attempt may also be made to increase biocompatibility through chemical (oxidation or hydrolysis) or physical modification. To increase cell adhesion and protein adsorption, water-soluble polymers may be added to the biomaterial surface. Bioactive molecules such as enzymes, proteins, peptides, or antibodies may also be coupled, as is the standard and routine practice, to the biomaterial surface to provide it with functionality[87]Other substances such as cytokines or growth factors which promote migration, proliferation, or overall function of cells used in therapy may be coupled.[62-65] Many types of biomaterials are being developed for bone tissue regeneration based on either demineralized bone matrix or in bladder submucosa matrix combined with poly(lactic-co-glycolic acid) (PLGA), which accelerates regeneration and promotes cell accommodation in in vivo bone formation . Advances in identification of the optimal characteristics of the matrix and an increased understanding of interactions between cells and biomaterials will condition development of future cell therapy protocols.[88]

Legal and regulatory issues of cell therapy

Cell therapy is one of the advanced therapy products (ATPs), together with gene therapy and tissue engineering. A regulatory framework is required for ATPs to ensure patient accessibility to

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products and governmental assistance for their regulation and control. Certainty, scientific reality and objectivity, and flexibility to keep pace with scientific and technological evolution are the characteristics defining an effective regulation [89].Aspects to be regulated mainly include control of development, manufacturing, and quality using release and stability tests; non-clinical aspects such as the need for studies on biodistribution, cell viability and proliferation, differentiation levels and rates, and duration of in vivo function; and clinical aspects such as special dose characteristics, stratification risk, and specific pharmacovigilance and traceability issues.[90,91].

Conclusions

In recent decades, a great interest has arisen in research in the field of stem cells, which may have important applications in tissue engineering, regenerative medicine, and cell- and gene therapy. There is however much to be investigated about the specific characteristics of efficacy and safety of the new drugs based on this type of cells.Cell therapy is based on transplantation of live cells into an organism in order to repair a tissue or restore lost or defective functions. Recent studies have shown that mesenchymal stem cells (MSCs) support hematopoiesis and immune response regulation and they represent an optimum tool in cell therapy because of their easy in vitro isolation and expansion and their high capacity to accumulate in sites of tissue damage, inflammation, and neoplasia. Induced pluripotent stem cells (iPSCs) from somatic cells are revolutionizing the field of stem cells. Cell therapy applications are related to the treatment of organ-specific diseases such as diabetes or liver diseases. Another relevant application of cell therapy is development of cancer vaccines based on dendritic cells or cytotoxic T cells, in order to induce natural immunity. Other applications, still in their first steps, include treatment of hereditary monogenic diseases such as hemophilia. Until widespread use of allogeneic protocols becomes established, thus overcoming the problems derived from immune rejection, biobanks represent the hope for the project of cell therapy to become a reality in the future; control of cell transformation is also particularly important for biosecurity of cell therapy products. In its early stages of development, and the market related to cell therapy is therefore highly immature, but the results achieved to date raise great expectations. Today, many pharmaceutical companies, including the big ones, are reluctant to enter this market because of the great investment required and because very hard competition is expected in the pharmaceutical market. Bioethical aspects will be required related to the scientific and therapeutic relevance and cost of cryopreservation

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over time, but specially with respect to embryos which may ultimately be used as source of embryonic stem cells, in which case the bioethical conflict may be further aggravated. Also, a regulatory framework will be required to ensure patient accessibility to products and governmental assistance for their regulation and control.

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