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A Review on Stem Cell Based Therapy and Emerging Clinical Roles in Medical Practice

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ABSTRACT

Recent advancements in stem cell technology open a new way for patients suffering from diseases and disorders that are still to be treated. Stem cell-based therapy, including human pluripotent stem cells (hPSCs) and Multipotency mesenchymal stem cells (MSCs), has now emerged as a key player in regenerative medicine. HPSCs are precise as self-renewable cell types conferring the ability to differentiate into various cellular phenotypes of the human body, plus three germ layers. This review seeks to familiarize the reader with the pretend of translation from an idea to clinical practice, in the context of stem cell products. We address some mandatory guidelines for clinical trial approval, including regulations and directives mounted by the Food and Drug Administration (FDA) of the United States, as well as those of the European Medicine Agency (EMA). Also, we review, summarize, and dispute regenerative medicine clinical trial studies registered on Stem cells are types of cells that retain unique ability to self-renew and to differentiate into more than one cell lineage. They are intended building blocks of tissues and organs. Over recent decades, they have been studied and applied for repair and regenerative medicine. One way to categorize these cells is based on their differentiation capacity.

INTRODUCTION

Cell-based therapy, especially stem cells, provides new confidence for patients suffering from incurable diseases where treatment approaches focus on organization of the disease not treat it. Stem cell-based therapy is an important branch of regenerative medicine with the eventual goal of enhancing the body repair machinery via stimulation, modulation, and guideline of the endogenous stem cell population and/or replenishing the cell pool near tissue homeostasis and regeneration. Since the stem cell definition was presented with their unique properties of self-renewal and differentiation, they have been subjected to numerous basic investigations and clinical studies and are defined as potential therapeutic agents. As the main agenda of regenerative medicine is associated with tissue regeneration and cellular replacement and to attain these targets, different types of stem cells have been used, with human pluripotent stem cells (hPSCs), multipotent stem cells and progenitor cells. Though, the emergence of private and unproven clinics that due to the effectiveness of stem cell therapy as "magic cells" has raised highly publicized concerns about the shelter of stem cell therapy.

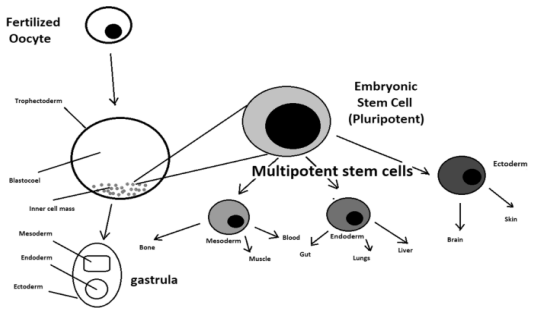

Fig.1 Cell Based Therapy

HISTORY

Stem cell therapy is a novel therapeutic approach that uses the unique properties of stem cells, including self-renewal and differentiation, to regenerate dented cells and tissues in the human body or replace these cells with new, healthy, and fully useful cells by delivering exogenous cells into a patient. Stem cells for cell-based therapy can be of autologous, also identified as self-to-self therapy, an approach consuming the patient's own cells, and allogeneic sources, which use cells from a healthy supporter for the conduct. The term "stem cell" was first used by the eminent German biologist Ernst Haeckel to describe the properties of fertilized eggs to provide rise to all cells of the organism in 1868. The history of stem cell

therapy started in 1888, when the description of stem cell was first coined by two German zoologists Theodor Heinrich Boveri and Valentin Haecker, who set out to categorize the discrete cell population in the embryo capable of differentiating to more specialized cells. In 1902, studies carried obtainable by the histologist Franz Ernst Christian Neumann, who was working on bone marrow research, and Alexander Alexandrowitsch Maximov demonstrated the existence of common progenitor cells that give rise to mature blood cells, a procedure also known as haematopoiesis. From this study, Maximov proposed the thought of polyblasts, which later were named stem cells based on their proliferation also differentiation by Ernst Haeckel. Maximov described a hematopoietic population presented in the bone marrow. In 1939, the first case crash described the transplantation of human bone marrow for a patient diagnosed with aplastic anemia. Twenty years advanced, in 1958, the first stem cell transplantation was attained by the French oncologist George Mathe to treat six nuclear researchers who were accidentally insecure to radioactive substances using bone marrow transplantation. An alternative study by George Mathe in 1963 shed light on the technical community, as he successfully showed bone marrow transplantation in a patient with leukemia. The first allogeneic hematopoietic stem cell transplantation (HSCT) was pioneered by Dr. E. Donnall Thomas in 1957. In this initial study, all six patients died, and only two patients exhibited evidence of transient engraftment due to the indefinite quantities and potential hazards of bone marrow transplantation at that time. In 1969, Dr. E. Donnall Thomas conducted the first bone marrow transplantation in the US, while the success of the allogeneic treatment continued exclusively. In 1972, the year marked the discovery of cyclosporine (the immune suppressive drug), the first achievements of allogeneic transplantation for aplastic anemia and acute myeloid leukemia stayed reported in a 16-year-old girl. From the 1960s to the 1970s, series of works conducted by Friendenstein and coworkers on bone marrow aspirates established the relationship between osteogenic differentiation and a minor subpopulation of cells derivative from bone marrow. These cells were later proven to be distinct from the hematopoietic population and to be able to proliferate quickly as adherent cells in tissue culture vessels. Another important breakthrough from Friendenstein's team was the detection that these cells could form the colony-forming unit when bone marrow was seeded as suspension culture subsequent by differentiation into osteoblasts, adipocytes, and chondrocytes, suggesting that these cells confer the capability to proliferate and differentiate into different cell types. In 1991, combined with the detection of human embryonic stem cells (hESCs), which will be discussed in the next section, the term "mesenchymal stem cells", before known as stromal stem cells or "osteogenic" stem cells,

was first coined in Caplan and extensively used to date.18 Starting with bone marrow transplantation 60 years ago, the journey of stem cell therapy has advanced throughout the years to develop a novel therapeutic agent of regenerative medicine to treat numerous incurable diseases, which will be reviewed and discussed in this review, including neurological disorders, pulmonary dysfunctions, metabolic/endocrine-related diseases, reproductive disorders, skin burns, and cardiovascular conditions).

STEM CELLS

Stem cells are the body's raw materials cells from which all various cells with specialized benefits are generated. Under the right conditions in the body or a laboratory, stem cells divide to form further cells called daughter cells. These daughter cells become to new stem cells or specialized cells (differentiation) with a further specific function, such as blood cells, brain cells, heart muscle cells or bone cells. No other cell in the body has the natural ability to produce new cell types.

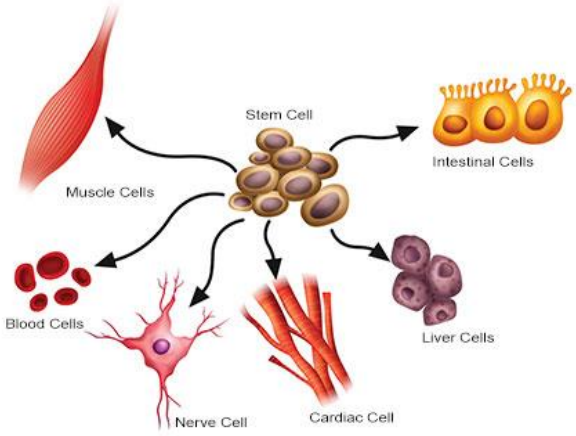

Fig 2 Stem Cells

CLASSIFICATION AND SOURCES OF STEM CELLS

Stem cells can be classified according to their source into four broad types, from embryos; from the foetus; from the neonates, and from the adult. Also, they can be classified according to their potency.

STEM CELLS CLASSIFICATION ACCORDING TO THEIR ORIGIN

Embryonic Stem Cells (ESCs) Embryonic stem cells:

Embryonic stem cells are pluripotent, self-renewing cells that can be concluded from either mouse or human blastocysts, they are taken from the very early stages of embryo progress after 4-5 days after fertilization. They can be stored in culture as undifferentiated cell lines and can be provoked to differentiate into any cell line. They can be separated into endoderm, mesoderm, and ectoderm embryonic germ layers, and also any type of somatic cells. They, therefore, trap a great capacity in tissue regeneration therapy.

Embryonic Germ Stem Cells:

Embryonic Germ (EG) cells are taken from the later stages of the embryo progress cells. They are concluded from Primordial Germline Cells (PGCs) in the early development. They are mainly dissented since the fetal tissue in narrow-window timing. The PGC-derived cells were pluripotent, albeit, it was not feasible to demonstrate pluripotency by generating the formation of teratomas in mice.

Fetal stem cells:

Fetal stem cells are primal cell types found in the organs of the fetuses. They are capable to discern into two varieties of stem cells: pluripotent stem cells and hematopoietic stem cells. Neural crest stem cells, fetal hematopoietic stem cells and pancreatic islet cells have been dissented in the fetuses. Human fetal stem cells have been utilized by many people, children and adults that are suffering from many of mankind’s very devastating diseases.

Umbilical cord stem cells:

Umbilical cord blood holds prevalent stem cells which differ from those of bone marrow and adult peripheral blood. Cord blood stem cells have exhibited to be multipotent as it being able to specialized into neurons and liver cells. Wharton’s jelly: Wharton’s jelly, which is the umbilical cord matrix, is reasoned to be a source of mesenchymal stem cells. These cells express typical stem cell markers, can be procreated for long times and can be induced to differentiate in vitro into neurons. Adult stem cells are any stem cells taken from mature tissue; they are initiated in the tissues of a fully developed child (whole embryo) or adult and can only generate a limited number of cell types. They have limited potential as compared to

the stem cells that concluded from embryos and foetuses since of the stage of development of these cells. They play a dynamic role in tissue repair, regeneration; and they are discussed to their tissue origin. Bone marrow is an abundant source of adult stem cells.

Mesenchymal stem cells:

Mesenchymal Stem Cells (MSCs) are a changed population of cells with the potential to differentiate into various somatic lineages. They were at first defined as adherent cells with a fibroblast-like appearance that can be discerned into osteocytes, chondrocytes, adipocytes, tenocytes and myocytes. MSCs can be secluded from the bone marrow and readily discreted from the hematopoietic stem cells due to their plastic adherence. They are utilized in tissue engineering and regenerative medicine. They are icon by long-storage without major loss of their potency.

Hematopoietic stem cells:

Hematopoietic stem cells are cells devising the self-renewing potential and the capacity to give rise to differentiated cells of all hematopoietic lineages. Therefore, they are transplanted for comprehensive healing of hematologic disorders and after high-dose chemotherapy in contradiction of malignant diseases.

Neural Stem Cells:

Neural stem cells are multipotent and self-replication cells, they are well-known in specialized molecular microenvironments in the adult mammalian brain. They can show the potential role in cellular therapy of the brain.

Gastrointestinal stem cells:

The stem cells of the gastrointestinal tract exist in a “niche” in the intestinal crypts and gastric glands. The mechanism and the direction of the diffusion of this changed clone in the gastrointestinal mucosa are hotly disputed, and central to this instance is the position and nature of the gastrointestinal stem cells. Epidermal stem cells: The mammalian epidermis is a quickly rejuvenating tissue that involves of three types of keratinocytes with varying differentiation potential.

Hepatic stem cells:

The liver has a strong regenerative capacity, using different modes of regeneration according to the type and extent of the injury. Mature liver cells can propagate to swap the damaged tissue permitting the recovery of the parenchymal function. Chronic liver injury gives augmentation to a potential stem cell compartment which is situated in the smallest branches of the intrahepatic biliary tree being activated, which called oval cell ductular reaction. These oval cells are consequent from the canal of Herring, which amplifies this biliary population prior to these cells being discerned into hepatocytes. In the human liver, the organization of the biliary tree is diverse, with the canal of herring extending to the proximate third of the lobule and so apparently requiring a name alteration from oval cells to hepatic progenitor cells.

Pancreatic stem cells:

Insulin-producing cells previously produced from pluripotent stem cells. The generation of these cells would provide a novel cell source for drug innovation and cell transplantation therapy in people suffering from diabetes. Insulin-producing beta-cells turnover every 40-50 days by procedures of apoptosis and the propagation and differentiation of the afresh islet cells from progenitor epithelial cells, which are positioned in the pancreatic ducts.

TYPES OF STEM CELLS ACCORDING TO THEIR DIFFERENTIATION

Stem cells can be classified according to their diversity potential as totipotent, pluripotent, multipotent, unipotent and oligopotent.

Totipotent stem cells:

Totipotency means that it has the total potential to give augmentation to all types of cells. Totipotent is the capacity of a single cell to slit and differentiate into all cell types in an organism and produce fertile offspring. Oocytes and sperm are the best differentiated cells in our body and they are adept of forming any tissue in the body.

Pluripotent stem cells:

Pluripotency is the ability of the cells to create any type of cells in the organism. They have been derived from the mouse embryo. All are talented of differentiating into cells

representative of a variety of adult tissue types in various assays, including embryo body, trachoma, and some can subsidise to mouse development in chimeras. Many changes are being recognized among pluripotent stem cell types, such as their morphology, gene expression profile and growth factor requirements.

Multipotent stem cells:

Multipotency means to those cells that can only give rise to cells of the tissue from which they are isolated. Unipotent stem cell: Adult stem cells are found in the tissues of the adults they produce a limited number of cell types and can repair damaged tissue by replacing specialized cells. Because of their restricted lineage, they were thought to be either multipotent, with the ability to differentiate into a limited range of cells or unipotent, with the ability to produce only one cell type.

Oligopotent stem cells:

Oligopotency means to those cells that can differentiate into only rare cell types, like lymphoid or myeloid stem cells.

SOURCE OF STEM CELLS

Bone marrow - the source of stem cells:

Stem cells are vital by self-renewing tissues to replace damaged and aging cells because of normal biological processes. Bone marrow has historically been the predominant harvesting site for stem cell gathering due to its accessibility, early identification as a source, and lengthy research history. Divorcing stem cell from bone marrow involves an invasive and painful surgical process and does come with a risk hospitalization or other complications. Patients also report increased post technical pain and pre-procedural anxiety when compared with other harvesting techniques. Bone marrow though has proved to be a denser cause of cells than other harvesting methods yielding 18 times more cells than peripheral blood progenitor cell harvesting techniques initially. As expertise and methods improved however, it was found that treating patients with a cytokine conduct prior to peripheral blood progenitor cell harvesting mobilized many of the preferred cells into the blood stream and drastically increased the efficiency of this technique, making it clinically viable. In a double blinded randomized study 40 patients underwent bone marrow and peripheral blood

progenitor cell gatherings and the yield of useable harvested cells were compared. It was originate that blood progenitor cell collection yielded significantly more useable stem cells and patients were able to undergo the collection process more frequently when compared to the bone marrow harvesting method. This coupled with the intrusiveness and risks associated with harvesting stem cells from bone marrow have improved peripheral blood progenitor cell collection popularity.

Overall, bone marrow as a reservoir of stem cells remains a clinical and research necessity related to its well implicit and documented history as a source of viable stem cells and track record of efficacy. Allowing to the European Group for Blood and Marrow Transplantation, only one fatal event was recorded stemming from the first 27,770 hematopoietic stem cell transplants obtained from bone marrow from 1993 to 2005. This undeniable pathway record of safety coupled with clinicians' experience performing bone marrow transplant procedures assurances the continued use of bone marrow as a source of HSC's for the near future.

Amniotic cells -source of stem cells:

Historically, the two most public types of pluripotent stem cells include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). Though, despite the many research efforts to improve ESC and iPSC skills here are still enormous clinical challenges. Two significant issues posed by ESC and iPSC technologies include the low survival rate of displaced cells and tumorigenicity. Recently, researchers have secluded pluripotent stem cells from gestational tissues such as amniotic fluid and the placental membrane. Human amnion-derived stem cells (hADSCs), plus amniotic epithelial cells and amniotic mesenchymal cells, are a relatively new stem cell source that has been found to have numerous advantageous characteristics.

For background, human amniotic stem cells begin emergent during the second week of gestation when a small cavity forms within the blastocyst and primordial cells lining this cavity are distinguished into amnioblasts. Human amniotic epithelial stem cells (hAESCs) are made when epiblasts differentiate into amnioblasts, whereas human amniotic mesenchymal stem cells (hAMSCs) are moulded when hypoblasts differentiate into amnioblasts. This differentiation happens prior to gastrulation, so amnioblasts do not fit to one of the 3 germ layers, making them theoretically pluripotent. Previously, pluripotency and immunomodulation are makings that have been thought to be mutually exclusive, as

pluripotency has traditionally been regarded as specifically limited to embryonic stem cells whereas immunomodulation has been a recognized things of mesenchymal stem cells. However, many recent studies have initiate that these two qualities coexist in hADSCs.

In recent years, hADSCs, with human amniotic epithelial stem cells (hAESCs) and human amniotic mesenchymal stem cells (hAMSCs) have been attractive cell sources for clinical trials and medical research, and have been shown to have returns over other stem cells types. These advantages include low immunogenicity and high histocompatibility, no tumorigenicity, immunomodulatory effects, and significant paracrine effects. Also, numerous studies have evaluated the proangiogenic ability of hADSCs. Interestingly, they found that hAMSCs were shown to enhance blood perfusion and capillary architecture when transplanted into the ischemic limbs of mice, signifying that hAMSCs stimulate neovascularization. Additionally, another advantage is that hADSCs are easier to obtain related to other stem cell bases, such as bone marrow stem cells (BMSCs).

Adipose tissue - source of stem cells:

Although the use of bone marrow stem cells (BMSCs) is now standard, dilemmas regarding harvesting techniques and the potential for low cell yields has driven researchers to search for other mesenchymal stem cell (MSCs) sources. One source that has been investigated is human adipose tissue. After enzymatic digestion of adipose tissue, a heterogenous group of adipocyte precursors are generated within a group of cells called the stromal vascular fraction (SVF). Adipose-derived stem cells (ADSCs) are found in the SVF. Studies have demonstrated that ADSCs possess properties typically associated with MSCs, and that they have been found to express several CD markers that MSCs characteristically express. ADSCs are multipotent and have been shown to differentiate into other cells of mesodermal origin, including osteoblasts, chondroblasts, myocytes, tendocytes, and more, upon in vitro induction. Additionally, ADSCs have demonstrated in vitro capacity for multi-lineage differentiation into specialized cells, like insulin-secreting cells.

A significant advantage of ADSCs over BMSCs is how easy they are to harvest. White adipose tissue (WAT) contains an abundance of ADSCs.The main stores of WAT in humans are subcutaneous stores in the buttocks, thighs, abdomen and visceral depots. Due to this, ADSCs can be harvested relatively easily by liposuction procedures from these areas of the body. Moreover, ADSCs make up as much as 1-2% of the SVF within WAT, sometimes

even nearing 30% in some tissues. This is a significant difference from the .0001-.0002% stem cells present in bone marrow. Given this difference in stem cell concentration between the sources, there will be more ADSCs per sample of WAT compared to stem cells per bone marrow sample, further demonstrating an easier acquisition of stem cells when using adipose tissue.

The number of ADSC clinical trials has risen over the past decade, and some have shown significant promise. They have demonstrated abilities to differentiate into multiple cell lines in a reproducible manner and be safe for both autogenetic and allogeneic transplantations. Several recent studies have demonstrated that ADSC-therapy may potentially be useful in the treatment of several conditions, including diabetes mellitus, Crohn's disease, multiple sclerosis, fistulas, arthritis, ischemic pathologies, cardiac injury, spinal injury, bone injuries and more.

One clinical trial conducted in 2013 investigated the therapeutic effect of co-infusion of autologous adipose-derived differentiated insulin-secreting stem cells and hematopoietic stem cells (HSCs) on patients with insulin-dependent diabetes mellitus. Ten patients were followed over an average of about thirty-two months, and they found that all the patients had improvement in C-peptide, HbA1c, blood sugar status, and exogenous insulin requirement. Notably, there were no unpleasant side effects of the treatment and all ten patients had rehabilitated to a normal, unrestricted diet and lifestyle.

In another 4-patient clinical trial in which ADSCs were used to heal fistulas in patients with Crohn's disease, full healing occurred in 6 out of the 8 fistulas with partial healing in the remaining two. 44 No complications were observed in the patients 12 months following the trial. Although these results are promising, the mechanism by which the healing took place remains unclear. When considering the properties of ADSCs, there are several factors that could have played a role in the healing, such as the result of paracrine expression of angiogenic and/or anti-apoptotic factors, stem cell differentiation, and/or local immunosuppression.

Umbilical Cord - source of stem cells:

Umbilical Cord stem cells can be drawn from a variety of locations including umbilical cord blood, umbilical cord perivascular cells, umbilical vein endothelial cells, umbilical lining, chorion, and amnion. Umbilical cord blood can be drawn with minimal risk to the donor, and

it has been used since 1988 as a source for hematopoietic stem cells. When compared to stem cells obtained from bone marrow, umbilical cord derived stem cells are much more readily available. With a birth rate of more than a 100 million people per year globally, there is a lot of opportunity to use umbilical cord blood as a source for stem cells.

The process of extracting the blood is very simple and involves a venipuncture followed by drainage into a sterile anti-coagulant-filled blood bag. It is then cryopreserved and stored in liquid nitrogen. There are quite a few benefits to utilizing umbilical cord stem cells rather than stem cells drawn from adults. One of the biggest benefits is that the cells are more immature which means that there is a lower chance of rejection after implantation in a host and would lead to decreased rates of graft-versus-host disease. They also can differentiate into a very wide variety of tissues. For example, when compared with bone marrow stem cells or mobilized peripheral blood, umbilical cord blood stem cells have a greater repopulating ability. Cord blood-derived CD34+ cells have very potent hematopoietic abilities, and this is attributed to the immaturity of the stem cells relative to adult derived cells. Studies have been done that analyze long-term survival of children with hematologic disorders who were transplanted with umbilical cord blood from a sibling donor. These studied revealed the same or better survival in the children that received umbilical cord blood relative to those that got transplantation from bone marrow cells. Furthermore, rates of relapse were the same for both umbilical cord blood and bone marrow transplant.

One of the unique features of stem cells taken from umbilical cord blood is the potential to differentiate into a wide variety of cell types. There are three different kinds of stem cells that can be found in the umbilical cord blood which include hematopoietic, mesenchymal, and embryonic-like stem cells. Not only can these cell types all renew themselves, but they can differentiate into many different mature cell types through a complex number of signaling pathways. This means that these cells could give rise to not only hematopoietic cells but bone, neural and endothelial cells. There are studies taking place currently to see if umbilical cord blood-derived stem cells can be utilized for cardiomyogenic purposes. Several studies have showed the ability to transform umbilical cord blood mesenchymal stem cells into cells of cardiomyogenic lineage utilizing activations of Wnt signaling pathways. Studies are also being conducted on the potential of neurological applications. If successful, this could help diseases such as cerebral palsy, stroke, spinal cord injury and neurodegenerative diseases. Given these cell's ability to differentiate into tissues from the mesoderm, endoderm and

ectoderm, they could be utilized for neurological issues in place of embryonic stem cells which are currently extremely controversial. There are currently studies involving in vitro work, pre-clinical animal studies, and patient clinical trials, all for the application of stem cells in neurological applications. There is big potential for the use of umbilical blood stem cells in the future of regenerative medicine.

Placental Tissue - Source of Stem Cells:

Placental tissue contains both stem cells and epithelial cells that can differentiate into a wide variety of tissue types which include adipogenic, myogenic, hepatogenic, osteogenic, cardiac, endothelial, pancreatic, pulmonary, and neurological. Placental cells can differentiate into all these different kinds of tissues due to lineages originating from different parts of the placenta such as the hematopoietic cells that come from the chorion, allantois, and yolk sac while the mesenchymal lineages come from the chorion and the amnion. It can be helpful to think of human fetal placental cells as being divided into four different groups: amniotic epithelial cells, amniotic mesenchymal stromal cells, chorionic mesenchymal stromal cells and chorionic trophoblast cells.

Human amniotic epithelial cells (hAECs) can be obtained from the amnion membrane where they are then enzymatically digested to be separated from the chorion. When cultured under certain settings hAECs are able to produce neuronal cells that synthesize acetylcholine, norepinephrine as well as dopamine. This ability would mean they have potential for regenerative purposes in diseases such as Parkinson's Disease, multiple sclerosis, and spinal cord injury. There is also research being done to utilize hAECs for ophthalmological purposes, lung fibrosis, liver disease, metabolic diseases, and familial hypercholesterolemia. Once cultured, hAECs have been shown to produce both albumin and alpha-fetoprotein as well as showing ability to store glycogen. Furthermore, they have been found to metabolize ammonia and testosterone. In more recent studies conducted in mouse models, these cells have been found to have therapeutic efficacy after transplantation for cirrhosis.

Mesenchymal stem cells are in many different tissues such as the bone marrow, umbilical cord blood, adipose tissue, Wharton's jelly, amniotic fluid, lungs, muscle and the placenta. Placental mesenchymal stromal cells specifically originate from the extraembryonic mesoderm. Human amniotic mesenchymal stromal cells (hAMSCs) and chorionic mesenchymal stromal cells (hCMSCs) have both been found to have very low levels of

HLA-A,B,C. This means that they have immune-privileged profiles for potential transplantation. Placental derived mesenchymal stem cells have been shown to have expression of CD29, CD44, CD105 and CD166 which is the same as adipose derived mesenchymal stem cells. These markers have been shown to have osteogenic differentiating abilities. An interesting element of placental mesenchymal stem cells is that their properties differ depending on the gestational age of the placenta. When cells are harvested at lower gestational ages, they show faster generation doubling times, better proliferative abilities, wider differentiation potential and more phenotypic stability than cells harvested from placental tissue that is considered to be at term. Furthermore, they have great potential to be used clinically. Placental mesenchymal stromal cells have been studied for use in treating acute graft-versus-host disease that was refractory to steroid treatment. Studies have shown that the 1-year survival rates in patients treated with placenta-derived stromal cells were 73% while retrospective control only showed 6% survival. Placenta-derived MSCs have also been found to aid in wound healing and could potentially be used to aid with certain inherited skin conditions such as epidermolysis bullosa.

FROM IDEA TO CLINICAL PRACTICE

From Idea to Preclinical Study:

If a researcher has an idea regarding regenerative medicine using stem cells that inspires their use in a study, it must first be evaluated. During the evaluation step, it is important to select the target disease and make sure that the mechanism causing the disease is understood. Disease-related mechanisms refer to the cellular and molecular processes by which a particular disorder is caused, and stem-cell-based therapies are considered a treatment method intended to compensate for the disruption caused by such mechanisms to finally restore the defective tissue. Multiple mechanisms cause diseases; however, stem cells, with their tremendous differentiation, self-renewal, angiogenesis, anti-inflammation, anti-apoptotic, and immunomodulatory potentials, as well as their capacity for induction of growth factor secretion and cell signaling, can affect these mechanisms. After subject evaluation, preclinical studies should be carried out to determine whether the idea has any potential to treat the disease, and the safety of the final product should be assessed in an animal model of the target disease. Preclinical studies are composed of in vitro and in vivo studies. In vitro experiments are performed with biological molecules and cells based on various hypotheses during the in vitro evaluation, and a new treatment method is assayed in

this controlled environment. In contrast, during in vivo studies, as controlling all biological entities is impossible, the new product may be affected by various factors and thus present different effects. The general purpose of a preclinical study is to present scientific evidence supporting the performance of a clinical study, and the following are required for a decision to move forward to clinical study: (i) the feasibility and establishment of the rationale (e.g., validation, separation of active ingredients in vitro, and determination of its mechanism in vivo), (ii) establishment of a pharmacologically effective capacity (e.g., secure initial dose verification), (iii) optimization of administration route and usage (e.g., safe administration method, repeated administration, and interval verification), (iv) identification and verification of the potential activity and toxicity (e.g., toxicity analysis according to single and repetitive testing), (v) identification of the potential for special toxicity (e.g., genetic, carcinogenic, immunological, and neurotoxic analyses), and (vi) determination of whether to continue or discontinue development of the treatment.

From Preclinical Study to Clinical Trial:

In principle, any idea regarding stem cell therapy should be assessed using comprehensive studies (i.e., in vitro and in vivo) before a clinical trial is considered, and the results of these studies should be proved by competent authorities. It can be easy during an in vitro study to create manipulative biological environments such as through the use of genetic mutation, drug testing, and pharmaceuticals, and it is easy to observe changes through the application of manipulated variables through living cells. However, given the many associated variables, such as molecular transport through circulating blood and organ interactions, it is hard to say whether such a study can completely mimic the in vivo environment. Before application in patients, in vivo experiments are conducted after in vitro experiments to overcome these weaknesses. Many researchers use rodents for in vivo studies, due to their anatomical, physiological, and genetic similarities to humans, as well as their other unique advantages including small size, ease of maintenance, short life cycle, and abundant genetic resources. The strength of in vivo studies is that they can supplement the limitations of in vitro studies, and the outcomes of their applications can be inferred in humans through the use of human-like biological environments. To establish in vivo experiments for stem cell therapies, the most correlated animal model should be selected depending on the specific safety aspects to be evaluated. Where possible, cell-derived drugs made for humans should be used for proof-of-concept and safety studies. Homogeneous animal models can also be utilized as the most

correlated systems in proof-of-concept studies. Furthermore, in vivo studies require ethical responsibilities and obligations to be upheld according to experimental animal ethics. In other words, unnecessary and unethical experiments must be avoided. Summing up the above, we can see that both in vitro and in vivo approaches are used in preclinical studies, which should be carried out before clinical trial applications based on various interests. Several factors must be considered in different in vitro and in vivo studies, including cell type determination, cell dose specification, route of administration, and safety and efficiency.

Stem Cell Source Determination:

As expectations rise for regenerative treatment through the application of stem cell therapies, the number of applications of various types and stem cell sources has increased, and stem cell therapies have diversified from autologous to allogenic to iPSCs. These stem cell treatments can vary in risk, depending on the cell manufacturing process, among other factors and in clinical experience, such that all types of stem cell treatments must be evaluated on the same basis. Therefore, the strengths and weaknesses of each type of stem cell should be identified to determine the maximum therapeutic effect of stem cells in various diseases. This will enable us to build disease-targeted stem cells by applying the appropriate stem cells to the appropriate diseases.

Cell Dose Specification:

The effective range of administration (i.e., dosage) of stem cells or stem-cell-derived products used in treatment should be determined through in vivo and in vitro studies. The safe and effective treatment capacity must be identified and, where possible, the minimum effective capacity must also be determined. When administered to vulnerable areas such as the central nervous system and myocardium, it has been reported that conducting normal dosage determination tests is unlikely. Thus, if the results of nonclinical studies can safely demonstrate treatment validity, it may be appropriate to conduct early human clinical trials with doses that may indicate therapeutic effects. An increasing dose of CD34+ cells (0.5 × 105 per mouse) has been shown to have positive effects, stimulating multi-lineage hematopoiesis at early stages and increasing the magnitude of reconstitution at post-transplant stages. Furthermore, improved T-cell reconstitution was correlated with higher cell doses of stem cells, compared to lower cell doses. However, a few studies related to acute myeloblastic leukemia (AML) have reported that high doses of HSCs were correlated with

restored function and rapid hematological and immunological recovery, but these results were not unconditional. In this study, a higher dose of HSCs (≥7 × 106/kg) resulted in poorer outcomes and a higher relapse rate than the lower dose of HSCs.

Route of Administration:

Stem cells have been extensively studied under various disease conditions, depending on their type and characteristics. At this time, the route of administration should not be overlooked in favor of the number of stem cells transplanted. Several reports have shown that engraftment ability typically has a lower rate of reaching target organs relative to the number of transplanted cells, and does not have a temporary longer duration. The methods of stem cell administration can largely be divided into local and systemic transmission. Local transmission involves specific injections through various manipulations and direct intra-organ injections, such as intraperitoneal (IP), intramuscular, and intracardiac injections. Systemic transmission uses vascular pathways, such as intravenous (IV) and intra-arterial (IA) methods. According to the publications in the literature, IV is the most common method, followed by intrasplenic and IP. In a liver disease model, IV was shown to be not only suitable for targeting the liver but also showed better liver regeneration effects than other routes of administration. Intracardial injection showed better cell retention in heart disease, while intradermal injection showed better treatment in skin diseases. Hence, we can determine that, in the context of these various diseases, the routes of administration should be different depending on the target organ. Many researchers have suggested that intravascular injection is a minimally invasive procedure, but it also poses a risk of clogged blood vessels, such that direct intravascular injection increases the risk of requiring open-air operations. Clinical trials have reported that the number of cells and treatment efficacy under the same conditions, as in preclinical studies, are not significant, but also differ in significance depending on the route of administration.

Manipulation of Cell Transplantation for Safety and Efficiency Improvement of Administration:

All medical treatments have benefits and risks. It is not particularly safe to apply these unproven stem cell treatments to patients. As expectations for regenerative treatment through stem cell therapies increase, the application of various administration pathways, including through the spinal cord, subcutaneous, and intramuscular, as well as the stem cell therapies

themselves, have been diversifying, from autologous to homogenous to iPS. These stem cell treatments can vary in risk, depending on the cell type manufacturing process among other factors, and they differ in clinical experience, such that all types of stem cell treatments must be evaluated on the same basis. Furthermore, it should only be in limited and justified contexts that stem cells that can proliferate and have all-purpose differentiation remain in a final product. Unfortunately, the only safe stem cells that have been employed in regenerative medicine so far are omnipotent stem cells, such as HSCs and MSCs, which are isolated from their self-origin. Unfortunately, potential clinical applications using iPSCs and ESCs face many hurdles, as they present higher risks, including the possibility of rejection, teratoma formation, and genomic instability. Hence, many researchers have attempted to overcome stem cell tracking for safety assessment. To check the engraftment and the remaining amount of stem cells, they have been labeled using BrdU, CM-Dil, and iron oxide nanoparticles, and visualized using Magnetic Resonance Imaging (MRI). A close analysis of the distribution patterns of administrative sites and target organs is required, as well as whether a distribution across the body is expected, and the organ that the cells are predicted to be distributed through should undergo a full-term analysis, including evaluation at administrative sites. To date, studies have reported assessments in the brain, lungs, heart, spleen, testicles, ovaries, kidneys, pancreas, bone marrow, blood, and lymph nodes, including areas of administration. Some researchers have carried out the detection of transplanted UC-MSCs delivered by IV injection in the lung, heart, spleen, kidney, and liver. According to their results, 7 of 21 planted cells were not detected in other organs, except the lung and liver, for 7 days. In the lung and liver, the detected cells persisted at least 7 days after the transplant.

From Clinical Trial to Clinical Practice:

Before a treatment is applied in humans (i.e., patients), preclinical study must involve checking whether the effect of treatment will be positive or negative and, if there are any negative effects, the researcher must check the safety possibilities at every step. Due to concerns relating to treatment using stem-cell-based products, deciding whether preclinical studies are sufficient for translating to clinical trials raises several issues that must be assessed by competent authorities. An application for a clinical trial should be submitted to the Food and Drug Administration (FDA), the European Medicine Agency (EMA), or another organization, based on the country. The FDA is responsible for certifying clinical

trial studies for stem-cell-based products in the United States. If a new drug is introduced to a clinical investigator that has not been approved by the FDA, an Investigational New Drug (IND) application may need to be submitted. The IND application includes data from animal pharmacology and toxicology studies, clinical protocols, and investigator information. A lack of preclinical support (e.g., in vitro and in vivo studies) can lead to required modification or disapproval. If the FDA has announced that an IND requires modifications (meaning that the application is intended to secure approval but has not yet been approved), the results of the preclinical studies were deemed insufficient or inadequate for translation to clinical trial study, such that further study must be completed, after which an amended IND should be submitted. The FDA has published guidelines for the submission of an IND in the Code of Federal Regulations (CFR). These regulations are presented in 21 CFR part 210, 211 (Current Good Manufacturing Practice (cGMP)), 21 CFR part 312 (Investigational New Drug Application), 21 CFR 610 (General Biological Product Standards), and 21 CFR 1271 (Human Cells, Tissues, and Cellular and Tissue-Based Products). These guidelines have been issued for the development of stem cell products with the highest standards of safety and potential effective translation to clinical trial studies. The FDA issued 21 CFR parts 210 and 211 to ensure the quality of the final products. The 21 CFR part 210 contains the minimum current good manufacturing practice (cGMP) considered at the stages of manufacturing, processing, packing, or holding of a drug, while the 21 CFR part 211 contains the cGMP for producing final products. The 21 CFR 211 includes FDA guidelines for personnel, buildings and facilities, equipment, and control of components, process, packaging, labelling, holding, and so on, all of which are critical for pharmaceutical production. The requirements for IND submission and conducting clinical trial studies, reviewed by the FDA in the 21 CFR part 312 (Investigational New Drug Applications), includes exemptions that are described in detail in 312.2 (general provisions). Such exemptions do not require an IND to be submitted, but other studies must present an IND based on 21 CFR part 312. The section, 21 CFR part 312, provides different information, including the requirements for an IND, its content and format, protocols, general principles of IND submission, and so on. In addition, the FDA describes the administrative actions of IND submission, the responsibilities of sponsors and investigators, and so on, in this section. The 21 CFR part 610 contains general biological product standards for final product characterization. The master cell bank (MCB) or working cell bank (WCB) used as a source for stem-cell-based final products must be tested before the release or use of the product in humans. The MCB and WCB should be tested for sterility, mycoplasma, purity, identity, and potency, among other tests based on the final

products (e.g., viability, stability, phenotypes), before use at the clinical level. The FDA provides all required information regarding general biological product standards in this section, including release requirements, testing requirements, labelling standards, and so on. The 21 CFR part 1271 focuses on introducing the regulations for human cells, tissues, and cellular and tissue-based products (HCT/P's), to ensure adequate control for preventing the transmission of communicable disease from cell/tissue products. Current Good Tissue Practice (GTP) is a part of 21 CFR part 1271, where the purpose of GTP is to present regulations for the establishment and maintenance of quality control for prevention of introduction, transmission, or spread of communicable diseases, including regulations for personnel, procedures, facilities, environmental control, equipment, and so on. The EMA is an agency in the European Union (EU) which is responsible for evaluating any investigational medical products (IMPs) in order to make sure that the final product is safe and efficient for public use. When planning to introduce a new drug for a clinical trial in Europe, one may be required to submit clinical trial applications to the EMA for IMPs. Clinical trial applications for IMPs include summaries of chemical, pharmacological, and biological preclinical data (e.g., from in vivo and in vitro studies). The EMA has presented different regulations to support the development of safe and efficient products for public usage, including Regulation (EC) No. 1394/2007, Directive 2004/23/EC, Directive 2006/17/EC, Directive 2006/86/EC, Directive 2001/83/EC, Directive 2001/20/EC, and Directive 2003/94/EC. Regulation (EC) No. 1394/2007 defines the criteria for regulation regarding ATMPs. Advanced therapy products (ATMPs) are focused on gene therapy medicinal products (GTMP), somatic cell therapy medicinal products (sCTMP), tissue-engineered products (TEP), and combined ATMPs, which refer to a combination of two different medical technologies. Regulation (EC) No. 1394/2007 includes the requirements to be used in the development, manufacturing, or administration of ATMPS. Directive 2004/23/EC, Directive 2006/17/EC, and Directive 2006/86/EC define standards for safety and quality, as well as technical requirements for donation, procurement, testing, preservation, storage, and distribution of tissue and cells intended for human applications. Directive 2001/83/EC applies to medicinal products for human use. Directive 2001/20/EC presents the regulations for the implantation of products in clinical trials in the EU; however, this directive will be replaced by regulation (EU) No. 536/2014. Regulation (EU) No. 536/2014 was adapted by the European Parliament in 2014, and provides regulation for clinical trials on medical products intended for human use. The new EU regulation comes into effect on 31 January 2022 and aims to coordinate all clinical trials performed throughout

the EU, using clinical trials submitted into CTIS (Clinical Trials Information System). The definition of regulation (EU) No. 536/2014 as a homogeneous regulation serves an important role in the EU, as all member states of the EU can be involved in multi-clinical trials using international coordination, thus allowing larger patient populations. Directive 2003/94/EC provides Good Manufacturing Practice (GMP) Guidelines in relation to medicinal products or IMPs intended for human use. All process and application requirements for the IMP application are present in the regulations and directives of the EMA. After presenting an IND/IMP to the regulatory authority responsible for clinical trial oversight (FDA or EMA), the application will be reviewed by the FDA/EMA criteria and, if assured of the protection of humans enrolled in the clinical study, the application will be approved by the investigational review boards (IRBs) in the United States or Ethics Committees (ECs) in the European Union. Clinical trial studies are composed of different steps where, at each step, products are assessed using different quality and quantity measurements by the responsible agency. An efficient clinical trial study should address the safety and efficiency of new stem cell products in each of the different steps, and it is important to complete each step based on defined instructions and regulations, as the results of previous steps are needed to move forward.

Challenges and Future Directions:

One of the most important issues regarding the introduction of a new product for use in humans through a clinical trial is the evaluation of its safety. Although many clinical trials have been performed using stem cells for the treatment of various diseases, as stem-cell based therapies are one of the newest groups of therapeutic products in medicine, it is very hard to introduce new products based on stem cells onto the market, as many different parameters must be evaluated. There are several concerns regarding stem-cell-based therapies, including genetic instability after long-term expansion, stem cell migration to inappropriate regions of the body, immunological reaction, and so on. However, all challenges depend on the type of stem cell (e.g., embryonic stem cell, adult stem cell, iPSc), type of disease, route of administration, and many other factors. Almost all researchers in the field of stem cell therapy believe that despite stem cells having great potential to treat disease through their intrinsic potential, unproven stem-cell-based therapies that have not been shown to be safe or effective may be accompanied by very serious health risks. To receive clinical trial approval from a competent regulatory authority, different tests must be

performed for each study phase, and the results of one study should not be generalized to another study. The FDA and EMA have defined different regulations to ensure that stem-cell-based products are consistently controlled using different preclinical studies (in vitro and in vivo). Based on these preclinical data, the FDA and EMA have the authority to approve a clinical trial study, as discussed in this review. Another challenge that researchers and companies face is the duration of a clinical trial study before a stem-cell-based product can be introduced onto the market. At present, hematopoietic progenitor cells are the only FDA-approved product for use in patients with defects in blood production, while other stem-cell-based products used in clinical trials have not yet been introduced to the market. In the past few years, several clinical trials have been conducted using stem cells, most of which have indicated the safety and high efficiency of stem-cell-based therapies. An attractive future option for regenerative medicine is the use of cell derivatives, including exosomes, amniotic fluid, Wharton's jelly, and so on, for the treatment of diseases. Recently, the safety and efficiency of these products have been evaluated and optimized in preclinical studies. In addition, regenerative medicine using modified stem cells and combinations of stem cells with scaffolds and chemicals to overcome stem cell therapy challenges and increase the associated efficiency are two important future directions of research. However, establishing a safe method for stem cell modification and moving this technology toward clinical trial studies requires many preclinical studies. The regenerative medicine market is developing and, due to encouraging findings in preclinical studies and predictable economic benefits, competition has increased between companies focused on the development of cell products. Therefore, government agencies, industries, individuals, universities, and private organizations have invested heavily in the development of the regenerative medicine market in recent years, such that we can be more hopeful about the future of stem-cell-based therapies.

CURRENT CLINICAL APPLICATIONS

Cardiovascular diseases:

The clinical applications of stem cell-based therapies for heart diseases have been recently discussed comprehensively in the reviews and therefore will be elaborated in this study as the focus discussions related to hPSCs and MSCs in the following sections. In general, the safety profiles of stem cell-based therapies are supported by a large body of preclinical and clinical studies, especially adult stem cell therapy (such as MSC-based products). However, clinical

trials have not yet yielded data supporting the efficacy of the treatment, as numerous studies have shown paradoxical results and no statistically significant differences in infarct size, cardiac function, or clinical outcomes, even in phase III trials. The results of a meta-analysis showed that stem cells derived from different sources did not exhibit any therapeutic effects on the improvement of myocardial contractility, cardiovascular remodelling, or clinical outcomes. The disappointing results obtained from the clinical trials thus far could be explained by the fact that the administered cells may exert their therapeutic effects via an immune modulation rather than regenerative function. Thus, well-designed, randomized and placebo-controlled phase III trials with appropriate cell-preparation methods, patient selection, follow-up schedules and suitable clinical measurements need to be conducted to determine the efficacy of the treatments. In addition, concerns related to optimum cell source and dose, delivery route and timing of administration, cell distribution post administration and the mechanism of action also need to be addressed. In the following section of this review, we present clinical trials related to MSC-based therapy in cardiovascular disease to discuss the contradictory results of these trials and analyse the potential challenges underlying the current approaches.

Digestive system diseases:

Gastrointestinal diseases are among the most diagnosed conditions in the developed world, altering the lives of one-third of individuals in Western countries. The gastrointestinal tract is protected from adverse substances in the gut environment by a single layer of epithelial cells that are known to have great regenerative ability in response to injuries and normal cell turnover. These epithelial cells have a rapid turnover rate of every 2–7 days under normal conditions and even more rapidly following tissue damage and inflammation. This rapid proliferation ability is possible owing to the presence of a specific stem cell population that is strictly compartmentalized in the intestinal crypts. The gastrointestinal tract is highly vulnerable to damage, tissue inflammation and diseases once the degradation of the mucosal lining layer occurs. The exposure of intestinal stem cells to the surrounding environment of the gut might result in the direct destruction of the stem cell layer or disruption of intestinal functions and lead to overt clinical symptoms. In addition, the accumulation of stem cell defects as well as the presence of Stem cell-based therapy: the history and cell source. The timeline of major discoveries and advances in basic research and clinical applications of stem cell-based therapy. The term “stem cells” was first described in 1888, setting the first

milestone in regenerative medicine. The hematopoietic progenitor cells were first discovered in 1902. In 1939, the first bone marrow transplantation was conducted in the treatment of aplasmic anemia. Since then, the translation of basic research to preclinical studies to clinical trials has driven the development of stem cell-based therapy by many discoveries and milestones. The isolations of "mesenchymal stem cells" in 1991 followed by the discovery of human pluripotent stem cells have recently contributed to the progress of stem cell-based therapy in the treatment of human diseases. Schematic of the different cell sources that can be used in stem cell-based therapy.

Liver diseases:

The liver is the largest vital organ in the human body and performs essential biological functions, including detoxification of the organism, metabolism, supporting digestion, vitamin storage, and other functions. The disruption of liver homeostasis and function might lead to the development of pathological conditions such as liver failure, cirrhosis, cancer, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and autoimmune liver disease (ALD). Orthotropic liver transplantation is the only effective treatment for severe liver diseases, but the number of available and suitable donor organs is very limited. Currently, stem cell-based therapies in the treatment of liver disease are associated with HSCs, MSCs, hPSCs, and liver progenitor cells. Liver failure is a critical condition characterized by severe liver dysfunctions or decompensation caused by numerous factors with a relatively high mortality rate. Stem cell-based therapy is a novel alternative approach in the treatment of liver failure, as it is believed to participate in the enhancement of liver regeneration and recovery. The results of a meta-analysis including four randomized controlled trials and six nonrandomized controlled trials in the treatment of acute-on-chronic liver failure (ACLF) demonstrated that clinical outcomes of stem cell therapy were achieved in the short term, requiring multiple doses of stem cells to prolong the therapeutic effects. Interestingly, although MSC-based therapies improved liver functions, including the model of end-stage liver disease score, albumin level, total bilirubin, and coagulation, beneficial effects on survival rate and aminotransferase level were not observed. A randomized controlled trial illustrated the improvement of liver functions and reduction of severe infections in patients with hepatitis B virus-related ACLF receiving allogeneic bone marrow-derived MSCs (BM-MSCs) via peripheral infusion. HSCs from peripheral blood after the G-CSF mobilization process were used in a phase I clinical trial and exhibited an improvement

in serum bilirubin and albumin in patients with chronic liver failure without any specific adverse events related to the administration. Taken together, an overview of stem cell-based therapy in the treatment of liver failure indicates the potential therapeutic effects on liver functions with a strong safety profile, although larger randomized controlled trials are still needed to assure the conclusions. Liver cirrhosis is one of the major causes of morbidity and mortality worldwide and is characterized by diffuse nodular regeneration with dense fibrotic septa and subsequent parenchymal extinction leading to the collapse of liver vascular structure.

Arthritis:

Arthritis is a general term describing cartilage conditions that cause pain and inflammation of the joints. Osteoarthritis (OA) is the most common form of arthritis caused by persistent degeneration and poor recovery of articular cartilage. OA affects one or several diarthrodial joints, such as small joints at the hand and large joints at the knee and hips, leading to severe pain and subsequent reduction in the mobility of patients. There are two types of OA: primary OA or idiopathic OA and secondary OA caused by causative factors such as trauma, surgery, and abnormal joint development at birth. As conventional treatments for OA are not consistent in their effectiveness and might cause unbearable pain as well as long-term rehabilitation (in the case of joint replacement), there is a need for a more reliable, less painful, and curative therapy targeting the root of OA. Thus, stem cell therapy has recently emerged as an alternative approach for OA and has drawn great attention in the regenerative field. The administration of HSCs has been proven to reduce bone lesions, enhance bone regeneration and stimulate the vascularization process in degenerative cartilage. Attempts were made to evaluate the efficacy of peripheral blood stem cells in ten OA patients by three intraarticular injections. Post-administration analysis indicated a reduction in the WOMAC index with a significant reduction in all parameters. All patients completed 6-minute walk tests with an increase of more than 54 meters. MRI Stem cell-based therapy for human diseases Hoang et al. 5 Signal Transduction and Targeted Therapy (2022) 7:272 analysis indicated an improvement in cartilage thickness, suggesting that cartilage degeneration was reduced post-administration. To further enhance the therapeutic potential of HSCT, CD34+ stem cells were proposed to be used in combination with the rehabilitation algorithm, which included three stages: preoperative, hospitalization, and outpatient periods. Currently, a large wave of studies has been directed to MSC-based therapy for the treatment of OA due to their

immune regulatory functions and anti-inflammatory characteristics. MSCs have been used as the main cell source in several multiple and small-scale trials, proving their safety profile and potential effectiveness in alleviating pain, reducing cartilage degeneration, and enhancing the regeneration of cartilage structure and morphology in some cases.

Cancer treatment:

Stem cell therapy in the treatment of cancer is a sensitive term and needs to be used and discussed with caution. Clinicians and researchers should protect patients with cancer from expensive and potentially dangerous or ineffective stem cell-based therapy and patients without a cancer diagnosis from the risk of malignancy development. In general, unproven stem cell clinics employed three cell-based therapies for cancer management, including autologous HSCTs, stromal vascular fraction (SVF), and multipotent stem cells, such as MSCs. Allogeneic HSCTs confer the ability to generate donor lymphocytes that contribute to the suppression and regression of hematological malignancies and select solid tumors, a specific condition known as “graft-versus_tumor effects’’.However, stem cell clinics provide allogeneic cell-based therapy for the treatment of solid malignancies despite limited scientific evidence supporting the safety and efficacy of the treatment. High-quality evidence from the Cochrane Library shows that marrow transplantation via autologous HSCTs in combination with high-dose chemotherapy does not improve the overall survival of women with metastatic breast cancer. In addition, a study including more than 41,000 breast cancer patients demonstrated no significant difference in survival benefits between patients who received HSCTs following high-dose chemotherapy and patients who underwent conventional treatment. Thus, the use of autologous T-cell transplants as monotherapy and advertising stem cell-based therapies as if they are medically approved or preferred treatment of solid tumors is considered untrue statements and needs to be alerted to cancer patients. Over the past decades, many preclinical studies have demonstrated the potential of MSC-based therapy in cancer treatment due to its unique properties. They confer the ability to migrate toward damaged sites via inherent tropism controlled by growth factors, chemokines, and cytokines. MSCs express specific C–X–C chemokine receptor type 4 (CXCR4) and other chemokine receptors (including CCR1, CCR2, CCR4, CCR7, etc.) that are essential to respond to the surrounding signals. In addition, specific adherent proteins, including CD49d, CD44, CD54, CD102, and CD106, are also expressed on the MSC surface, allowing them to attach, rotate, migrate, and penetrate the blood vessel lumen to infiltrate the damaged tissue.

Similar to damaged tissues, tumors secrete a wide range of chemo attractant that also attract MSC migration via the CXCL12/CXCR4 axis. Previous studies also found that MSC migration toward the cancer site is tightly controlled by diffusible cytokines such as interleukin 8 (IL-8) and growth factors including transforming growth factor-beta 1 (TGF-β1), platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF-2), vascular endothelial growth factor (VEGF), and extracellular matrix molecules such as matrix metalloproteinase_2 (MMP-2).Once MSCs migrate successfully to cancerous tissue, accumulating evidence demonstrates the interaction between MSCs and cancer cells to exhibit their protumour and antitumor effects, which are the major concerns of MSC-based therapy. MSCs are well-known for their regenerative effects that regulate tissue repair and recovery. This unique ability is also attributed to the protumour functions of these cells. A previous study reported that breast cancer cells induce MSC secretion of chemokine (C–C motif) ligand 5 (CCL-5), which regulates the tumor invasion process. Other studies also found that MSCs secrete a wide range of growth factors (VEGF, basic FGF, HGF, PDGF, etc.) that inhibits apoptosis of cancer cells.

CONCLUSION

In recent years, regenerative medicine has become a promising treatment option for various diseases. Due to their therapeutic potential, including the inhibition of inflammation or apoptosis, cell recruitment, stimulation of angiogenesis, and differentiation, stem cells can be seen as good candidates for regenerative medicine. In this review study, we present a Stem cells are diverse in their differentiation capacity as well as their source of origin, there are similarities and differences when these cells are extracted from different sources, and a general overview of the translation of stem cell therapy. Multiple mechanisms causing disease could be reversed by stem cells, due to their tremendous therapeutic potential and also it exhibits different functional activities and treatment effectiveness across a wide range of human diseases. For these reasons, extensive research is still needed in this area of medicine to pave the way for new developing therapy modalities.

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