Chapter 10

Human Placenta-Derived Mesenchymal Stromal Cells: A Review from Basic Research to Clinical Applications

Paz de la Torre, María Jesús Pérez-Lorenzo and Ana I. Flores

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76718

Abstract

Placenta-derived mesenchymal stem/stromal cells (PMSC) present several aspects that make them more attractive as cellular therapy than their counterparts from other tissues, such as MSC from bone marrow or adipose tissue in regenerative medicine. Placenta-derived MSC have been used to treat a variety of disorders, such as, cancer, liver and cardiac diseases, ulcers, bone repair, and neurological diseases. Placenta-derived MSC are relatively new types of MSC with specific immunomodulatory properties and whose mechanisms are still unknown. Placenta-derived MSC secrete some soluble factors that seem to be responsible for their therapeutic effects, i.e., they have paracrine effects. On the other hand, Placenta-derived MSC can also serve as cellular vehicles and/or delivery systems for medications due to their migration capacity and their tropism for injury sites. Nanotechnology is an important field, which has undergone rapid development in recent years for the treatment of injured organs. Due to the special characteristics of placenta-derived MSC, the combination of these cells with nanotechnology will be a significant and highly promising field that will provide significant contributions in the regenerative medicine field in the near future.

Keywords: placenta, mesenchymal stromal cells, immunoregulation, regenerative medicine, nanotechnology, cancer, neurodegeneration, vascular, bone, cartilage, liver, urology, intestinal

1. Introduction

1.1. Structure and function of human placenta

Human placenta is an indispensable organ during pregnancy for supporting the development of the fetus. The placenta is a unique organ since it is a multicellular barrier, in which

both maternal and fetal cells coexist. Placenta performs functions of metabolic exchange and endocrine regulation between two genetically distinct individuals, the mother and the fetus, while maintaining immunological tolerance between them [1, 2].

The term placenta derives from the latin and means "flat cake" because of its discoid shape. At the end of pregnancy, it is about 15–20 cm in diameter, 2–3 cm thick, and 500 g in weight, that is, 1/6 of the fetal weight.

The placenta is constituted by structures of fetal origin, such as, the placental disk, the fetal membranes, divided in amniotic and chorionic membranes, and the umbilical cord. The placenta is also composed by a membrane of maternal origin termed the decidua that originates from the endometrium. The functional unit of the placenta is the chorionic villosity that forms the border between maternal and fetal blood during pregnancy (**Figure 1**).

1.2. Placenta development

Placenta development is a continuous process that starts during early embryological stages, even before gastrulation occurs. Four to five days after fecundation, the morula (solid mass of cells called blastomers) has reached the uterus. The appearance of a fluid-filled inner cavity marks the transition from morula to blastocyst and is accompanied by cellular differentiation: the surface cells become the trophoblast (giving rise to extraembryonic structures, including the placenta and the umbilical cord) and the inner cell mass gives rise to the embryo [3]. Just before the implantation into the endometrium, the internal cell mass or embryoblast, goes through important changes such as cellular reorganization that gives place to a top layer, the epiblast and a bottom layer named hypoblast or primitive endoderm. Some extraembryonic tissues such as the amnion derive from the epiblasts that delimit the amniotic cavity that hosts the embryo during pregnancy. Because of the increase in production of amniotic liquid during gestation, the amnion will expand, and merge with the trophoblast to give rise to the amnion-chorionic membrane. Another of the earliest differentiation events in human embryogenesis takes place in the trophoblast with the development of the external syncytiotrophoblast

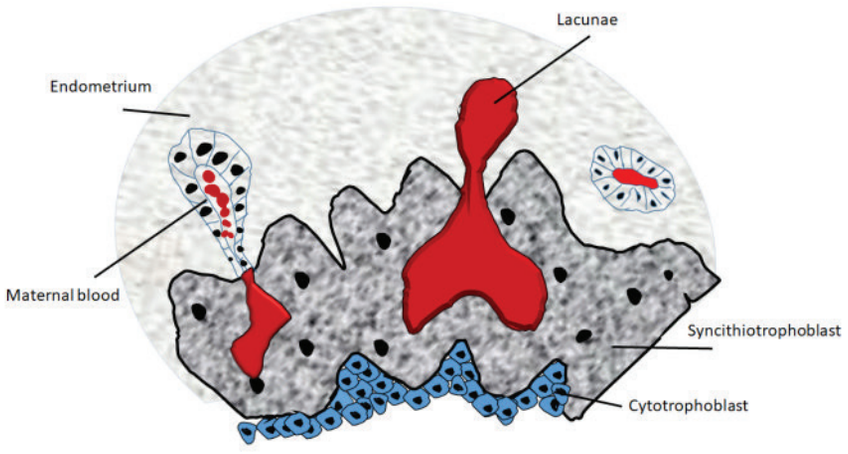

Figure 1. First stage in the interaction between fetal and maternal blood circulation. The syncytiotrophoblast erodes maternal vessels.

and the internal cytotrophoblast. The cytotrofoblast is constituted by highly proliferative mononucleated cells. Syncytiotrophoblast is formed by fusion of cytotrophoblastic cells and has high invasive capacity. This syncytium is responsible for the implantation or anchorage of the blastocyst within the uterine walls.

The lytic activity of the syncytiotrophoblast, which is responsible for the degradation of the matrix of the endometrium, reaches the uterine capillaries, eroding them. As a result of vascular damage, maternal blood comes out to the syncytiotrophoblast where it forms lacunae; this lacunar stage is the first one toward a fetomaternal circulation. At the same time, the epithelial-like cells of the cytotrofoblast, which have continued proliferating, form accumulations that project toward the syncytiotrophoblast forming the chorionic villi that penetrate the decidua basalis [4]. These finger-like structures (cytotrophoblast covered with syncytiotrophoblast) are invaded by an extraembryonic mesoderm that, in the fourth week after fertilization, gives rise to blood vessels within each villi which makes possible the establishment of the interaction between the fetal circulation, in these embryo vessels, and the maternal blood contained in the trophoblastic lacunae (**Figure 1**). The different layers of the trophoblast (the cytotrophoblast and the syncytiotrophoblast), the basal membranes of the fetal vessels, and the vascular endothelium of these vessels constitute the placenta barrier that regulates the metabolite exchange between both circulations (fetal and maternal). It has been estimated that this exchange surface is about 5 m^2 at week 28 of gestation and reaches 10–11 m^2 at term [5]. Moreover, this barrier undergoes a progressive thinning throughout pregnancy going from 10 microns at the beginning to 1 or 2 microns at the end of the gestation [6]. The umbilical cord connects placenta to the fetus. It is a narrow tube that contains two arteries and one vein to transport metabolites between mother and fetus.

1.3. Regenerative medicine and placenta

Regenerative medicine is an interdisciplinary field within translational medicine whose purpose is to heal or replace damaged tissues or organs as a result of age, illness or trauma. It may involve the transplantation of stem cells that will repair the damaged tissue, stimulate the body's own repair processes or serve as delivery-vehicles for therapeutic agents such as genes, cytokines, or therapeutic drugs.

Stem cells are unspecialized cells that have the capacity to renew themselves or differentiate toward more specialized cells. The proliferation of stem cells is indispensable for the maintenance of the stemness niche. The differentiation is the process by which, under certain physiological or experimental conditions, unspecialized cells are induced to become tissue- or organ-specific cells. The differentiation potential of stem cells is essential during the development of the embryo. In the adult, the main function of stem cells is the maintenance of the tissue homeostasis acting as an internal repair system.

Both embryonic and adult tissues are sources of stem cells with therapeutic potential. However, embryonic stem cells have some limitations in clinical practice, such as ethical concerns, difficulty in obtaining, and tumorigenicity. Adult stem cells have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, adipose tissue, skeletal muscle, skin, teeth, heart, gut, liver, and placenta. Though the number of stem cells

is very small in many adult tissues, their isolation involves several risks and, once removed from the body, the cells have a limited capacity of proliferation and differentiation, making the generation of large quantities of stem cells difficult.

The placenta is a reservoir of stem cells with several advantages. What makes placenta such an interesting tissue for regenerative medicine? Placenta is spontaneously expulsed at birth, making the use of invasive methods unnecessary as in the case of other sources of adult stem cells. It is considered a medical waste and there are no ethical concerns in its use, unlike using embryonic stem cells [7]. Placenta is a high-yielding source of stem cells compared to other sources such as bone marrow and adipose tissue where the cell recovery decreases with donor age [8]. Versatility and differentiation potential of placental cells is very high probably due to their primitive origin [9]. Furthermore, pregnancy is an example of "tolerated allograft" and placenta is the immunoregulatory organ at the maternal-fetal interface [10]. Placenta is an immunoprivileged organ, and cells isolated from placenta display low immunogenicity in vitro [11] and in vivo [12] when xenotransplanted in immunocompetent animals. The feasibility of placental cells for allogeneic transplantation has been demonstrated [13].

In regenerative medicine, the effects of stem cells are not only restricted to cell or tissue restoration but also to transient paracrine actions. This paracrine action is related to factors produced and secreted by stem cells that will control the injury, modulate the immune responses, and promote self-repair in the surviving injured tissue [14]. Placenta plays a fundamental role in fetomaternal tolerance and this would explain why placenta-derived stem cells have an additional advantage over other stem cells in terms of immunomodulation [15].

Multiple mechanisms underlie maternal tolerance during pregnancy. Fetal and, in particular, placental tissues contribute to its immunoprivileged and immunoregulatory environment. Placental cells are characterized by the absence of MHC class II antigens that normally mediate graft rejection [16]. Placental cells not only express a low level of the highly polymorphic forms of the MHC class I antigens but also express the nonclassical form HLA-G that may play a role in the suppression of immune responses and contribute to maternal-fetal tolerance [17, 18]. Furthermore, through the release of hormones [19], cytokines [20], and soluble forms of MHC antigens, placental cells deviate maternal immune responses toward immune tolerance. Therefore, the cells of the innate immunity of the mother acquire a suppressive profile characterized by a diminished production of pro-inflammatory cytokines. In addition, the B cells and many T cells disappear, leaving the regulatory T cells (Tregs) as the major T-cell subpopulation, with both, immune suppressive and anti-inflammatory characteristics [21].

1.4. Placenta-derived stem cells

Different populations of cells with features of stem/progenitor cells have been isolated from placenta: hematopoietic, epithelial, trophoblasts, and mesenchymal cells.

Placenta is a hematopoietic organ since it harbors a large pool of hematopoietic stem cells (HSC) that possess functional properties of true HSC. Placenta-derived HSC can differentiate into all types of mature blood cells and are able to sustain the hematopoiesis during the life of the embryo. Placental HSC activity declines toward the end of gestation, possibly reflecting

mobilization of placental HSC to the fetal liver and other developing hematopoietic organs within the embryo, such as thymus, spleen, and bone marrow [22].

The three layers of the placenta, such as the amnion, the chorion, and the decidua, are sources of stem cells. The amniotic layer is composed of a single-cell epithelial layer and a deeper mesodermal layer derived from the epiblast and hypoblast, respectively [23]. The chorion sheet is composed of the inner chorionic mesoderm similar to the mesenchymal region of the amnion and an outer layer of trophoblastic origin. The decidua, the uterine component of the placenta, is also a source of cells of mesodermal origin.

Amniotic epithelial cells (AEC) are very valuable stem cells for regenerative medicine. They have stem cell molecular markers such as OCT-4, Nanog, SOX-2, and Rex-1 (23). AEC do not have telomerase reverse transcriptase, show a stable karyotype, and do not originate tumors when injected. Amnion does not express MHC class II antigens, so AEC can elude the immune system. AEC can also modulate the immune system through an inhibition of the proliferation of T- and B-cells. In addition, AEC inhibit inflammation, as has seen in vitro [24].

Chorion trophoblastic cells (CTC) represent a mixed and still poorly characterized population of stem cells and there are no reliable methods to isolate them [25], and also, no consistent marking for identifying this population of cells [26].

Most of stem cells isolated from the placental tissues are cells of mesodermal origin and are named amnion mesenchymal stromal cells (AMSC), chorion mesenchymal stromal cells (CMSC), chorionic villi mesenchymal stromal cells (CV-MSC), and decidua mesenchymal stem cells (DMSC) [9, 27, 28] depending on the layer of origin. Inside the umbilical cord, there is a connective tissue that surrounds the umbilical vein and the two umbilical arteries. This tissue, also known as Wharton's jelly, is a rich source of mesenchymal stromal cells called umbilical cord mesenchymal stem cells (UC-MSC) [29]. They are all considered true mesenchymal stromal cells (MSC), as they meet the three minimal criteria proposed by the International Society for Cellular Therapy [30]. First, placenta-derived MSC exhibit plastic adherence in culture. Second, they express a specific set of cell surface markers, such as CD105, CD73, and CD90, and do not express hematopoietic markers including CD34, CD45 and CD14 or CD11b, CD79a or CD19, and HLA-DR. Third, they have the ability to differentiate in vitro into different mesodermal cell lineages including adipocytes, chondrocytes, and osteoblasts. In addition, AMSC and CMSC are from fetal origin according to the first international workshop on placenta-derived stem cells [31].

Cells with properties of mesenchymal stromal cells have also been isolated from the amniotic fluid (AF) which is used to perform the evaluation of karyotyping and prenatal diagnostic testing. AF is a source of MSC that could be used as autologous cellular therapy for perinatal disorders [32]. These AF-MSC can be easily isolated, have minimal ethical objections, high renewal activity, multiple differentiation capacity, and maintain genetic stability in culture [33].

In this chapter, we will refer to placenta-derived mesenchymal stromal cells as placenta mesenchymal stromal cells (PMSC) regardless of the placenta region where they were isolated.

1.5. Placenta-derived mesenchymal stromal cells

Mesenchymal stromal cells (MSC) can be isolated from virtually all adult tissues in the body, although not always in large quantities. They are thought to be a precursor cell population capable of reconstituting all the cellular elements that comprise the supportive stromal tissue in each organ [34]. First described in bone marrow as a subset of non-hematopoietic cells [35], they have become the paradigm cell in regenerative medicine. MSC are the most widely studied cell type in both preclinical and clinical trials. The advantages of MSC include ease of isolation and subsequent maintenance in culture, high expansion capacity, high plasticity, and tissue repair activity. The restorative activity of MSC is not necessarily by the replacement of dead or damaged cells, but also, by paracrine actions that mediate immune-regulation and promote cell growth and/or differentiation (**Figure 2**). Besides, MSC do not form teratomas after transplantation, ensuring safety to the host and, their low immunogenicity makes them suitable for allogeneic transplantation. Furthermore, these cells have the ability to migrate to inflammatory microenvironments [36] and tumors [12, 37], where they play an active role inducing many processes, such as angiogenesis and wound healing, mainly in a paracrine manner [38]. This feature provides an important therapeutic advantage to MSC since they can be injected via systemic infusion and can be used as vehicles for the delivery of drugs such as anticancer agents to the tumor site.

The use of placenta as a source of MSC has several advantages with respect to other adult MSC. Besides the ease of extraction of MSC from the placenta without invasive methods, the isolated MSC represent a more homogeneous and primitive population [9, 39]. The last feature is associated with a higher proliferative rate in culture compared to bone marrow MSC [40]. This fact makes it possible to achieve a greater number of cells in fewer passages

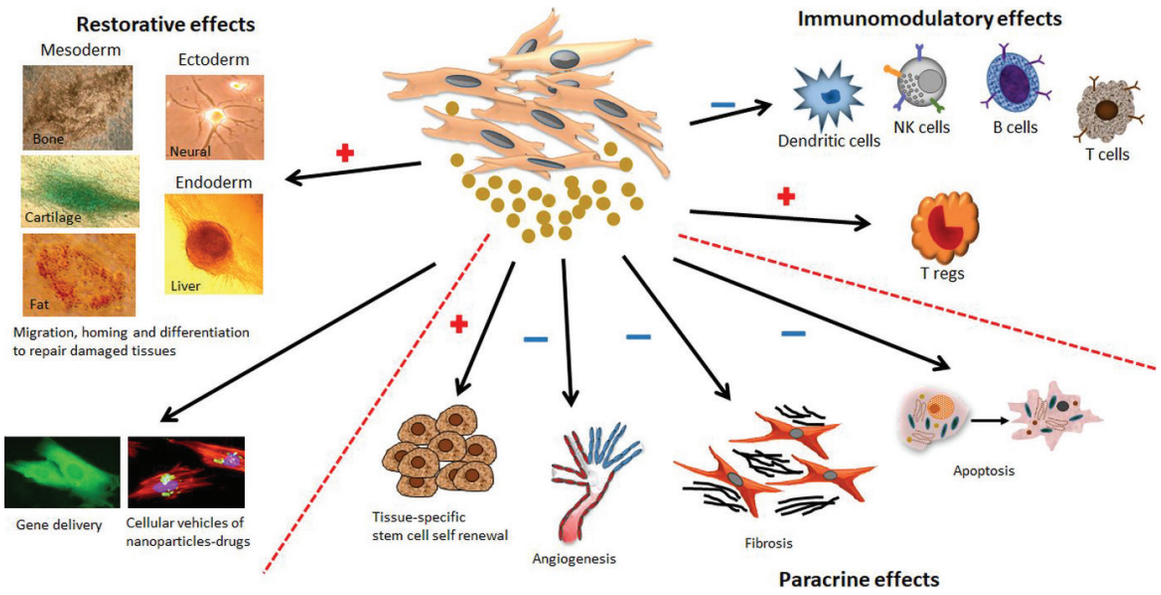

Figure 2. PMSC mechanisms of action. PMSC can migrate, home, and differentiate into tissue specific cells to repair injured tissue, transport restorative genes and used as a cellular vehicles of therapeutic agents. PMSC also exert their actions through paracrine effects and have immunomodulatory properties.

http://dx.doi.org/10.5772/intechopen.76718

reducing the risk of ex vivo senescence influencing gene expression and resulting in aging phenotype [41, 42]. The senescent state needs to be taken into account for quality control of PMSC in cellular therapy. In addition, the clinical efficacy and safety of PMSC could be higher, compared to other sources of MSC, since PMSC are younger cells that have been exposed less time to harmful agents, such as reactive oxygen species (ROS), chemical and biological agents, and physical stressors [43]. Also, PMSC have a limited capacity to grow in culture related to low telomerase activity, which is also lost during proliferation, making them a safe product to be used in regenerative medicine [9]. Moreover, PMSC could be advantageous with respect to migratory properties and homing capacities into damaged tissues. Homing of MSC is basically dependent on the release of chemoattractants by the injured tissue and the expression of chemokine receptors on the MSC membrane. For extravasation into tissue, MSC have to attach to and migrate through the endothelium. Several integrins and other adhesion molecules are known to be expressed on MSC. Dependence on the VLA-4/VCAM-1 (very late antigen-4/vascular cell adhesion molecule-1) axis for MSC adherence to endothelial cells has been demonstrated [44]. PMSC have a higher expression of VLA-4 compared to bone marrow MSC suggesting that PMSC may have enhanced properties for homing to damaged tissue [45].

2. Therapeutic applications of placenta mesenchymal stromal cells (PMSC) in preclinical models

Stem cell therapies are expected to provide substantial benefits to patients suffering a wide range of pathologies. The plasticity and pleiotropic properties of PMSC that include immunomodulation and inflammation control, angiogenesis, neuroprotection, and antiapoptosis, among others, have been widely evaluated at the preclinical level [9, 46, 47].

2.1. Use of placental mesenchymal stem/stromal cells in cardiovascular diseases

2.1.1. Myocardial infarction

Myocardial infarction (MI) is a major cause of death and disability worldwide. MI occurs when there is an interruption in blood flow to the heart muscle followed by heart ischemia. Since regeneration of heart muscle is virtually absent, damaged myocardium after infarct is replaced by scar tissue leading to reduced cardiac function. PMSC transplantation is a promising strategy to restore cardiac function and reduce myocardial fibrosis in MI due to their angiogenic and immunosuppressive properties.

PMSC have the potential to differentiate into cardiomyocytes, and exhibit spontaneous beating under in vitro conditions suggesting that they can therapeutically act in the cardiac repair process [9, 48, 49]. Several groups have investigated the effects of PMSC when transplanted in animal models of MI. PMSC injected into rat hearts after the induction of a MI showed integration into cardiac tissues and in vivo transdifferentiation into cardiomyocytes [48]. The CXCR4 chemokine receptor and its ligand, stromal cell-derived factor (SDF-1)

axis (CXCR4-SDF1) is the main pathway mediating migration of MSC toward injured tissues. Since it has been shown that chemokine receptor type 4 (CXCR4) is greatly induced in PMSC by hypoxia, a high chemotactic response of PMSC to the ischemic microenvironment of the infarcted heart is expected [50]. Intravenous injection of PMSC in a rat model of infarct showed a sustained cardiac function over 32 weeks from injury [51]. Preconditioning PMSC by hyaluronan mixed ester of butyric and retinoic acid (HBR) potentiates their reparative capacity. Transplantation of preconditioned PMSC in pigs produced a significant reduction in scar size, higher myocardial perfusion and glucose uptake, enhanced capillary density, and decreased fibrous tissue [52]. The paracrine potential of conditioned medium (CM) of PMSC has also been evaluated. Injection of PMSC-CM limited infarct size and cardiomyocyte apoptosis, while promoting capillary density in the infarct border area in a rat model of ischemia/reperfusion [53].

2.1.2. Critical limb ischemia

Critical limb ischemia (CLI) is the advanced stage of peripheral artery disease (PAD) with progressive stenosis, and ultimately the obstruction of peripheral arteries. The consequences of the markedly reduced blood flow to the lower limbs are pain at rest, nonhealing ulcers, and gangrene. The risk factors of PAD are advanced age, hyperlipidemia, hypertension, and mainly diabetes. Unfortunately, amputation, in many cases, is the only therapeutic option for CLI as blood capillaries cannot be corrected, and restenosis of vessels is produced.

Preclinical studies have reported benefits of cell therapy in neovascularization in several mouse models of hindlimb ischemia. PMSC have demonstrated pro-angiogenic effects when intramuscularly injected into the ischemic region of the affected limb, improving blood flow and promoting new vessel formation [54–56]. Similar results have been described in a diabetic nude rat model [57]. Moreover, CM from the PMSC also had pro-angiogenic action in a mouse hindlimb ischemic model, comparable to the PMSC transplanted group in the same study, revealing that PMSC action resulted primarily from a paracrine action of the angiogenic factors released from the PMSC [55]. However, in another study, cells were more efficacious than cell lysate in rescuing blood flow, probably indicating the importance of prolonged paracrine effect for maximal blood flow recovery [57].

2.1.3. Stroke

Stroke is an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH), and is a major cause of disability and death worldwide. Thrombolysis is the most commonly used therapeutic approach although most patients fall outside of the clinical time window for effective treatment.

Experimental data show that stem cell therapy can limit neuronal degeneration and improve the functional outcome. The neuroprotective action of PMSC has been demonstrated in a rat model of stroke. Intravenous administration of PMSC, 4 hours after the injury, resulted in a significant improvement of functional outcome and significant decrease of lesion volume, correlating with increased vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and brain-derived neurotrophic factor (BDNF) levels in the ischemic brain compared to controls [58].

2.2. Use of placental mesenchymal stem/stromal cells in cancer

Cancer is one of the main problems in public health worldwide. Despite great progresses having been made in understanding the molecular basis of cancer, and the rapid advances in diagnosis, the efficacy of current treatment strategies is limited and mortality is still high. Stem cell-based treatments have been extensively explored for their possible potential to treat various cancers. Tumor microenvironment resembles a wound environment as tumors are considered as unhealed wounds [60]. Inflammatory and wound microenvironments induce migration of PMSC [36, 61]. Due to the characteristic of placenta-derived MSC, these cells represent an important tool for their use in anticancer therapies. First, PMSC can migrate and engraft into the tumor site and directly affect tumor biology through paracrine signaling. Second, PMSC could be used for the specific delivery of drugs to tumors thus reducing the doses administered and the side effects. Third, PMSC can also be genetically modified to give a stable expression of antitumor factors specifically in the tumor.

Placenta-derived MSC have an intrinsic tropism for sites of injury regardless of tissue or organ. Furthermore, it has been shown that PMSC and CM from PMSC are able to inhibit the proliferation of several tumor cell lines [62]. Moreover, PMSC have an antitumor effect in vivo, inhibiting tumor progression when were intravenously injected in a rat model of mammary cancer [12]. Similarly, PMSC showed antitumor effects in vivo when previously expanded in the presence of tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) [63] and when engineered to deliver growth factors to the tumor site, such as, pigment epithelium-derived factor [64], or endostatin [65].

2.3. Use of placental mesenchymal stem/stromal cells in neurological diseases

Neurodegeneration involves a progressive and irreversible loss of neurons. Alzheimer's, Parkinson's, and multiple sclerosis are some of the more studied neurodegenerative syndromes. The neuromuscular disorder amyotrophic lateral sclerosis (ALS) is a degenerative process caused by motor neuron loss. To date, there is no cure for these diseases. Cell therapy with stem cells arises as a therapeutic alternative based, either on the replacement of the lost neurons, or on a neuroprotective action through release of neurotrophic factors. PMSC are able to differentiate in vitro into several neural lineages, including neurons [9, 66], oligodendrocytes [66], glial cells [67], and dopaminergic neurons [68].

2.3.1. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease associated with a specific loss of dopaminergic neurons in the substantia nigra and depletion of dopamine levels in the striatum. The main therapeutic objective in PD is the recovery of dopaminergic neurotransmission in the striatum. Cellular replacement has been emerged as a suitable therapeutic strategy. First-trimester human PMSC differentiated to neural progenitors and transplanted into the striatum of a rat model of PD, underwent dopaminergic differentiation and showed an attenuation of the symptoms [69]. PD motor pathology is also accompanied by other disabilities, such as, mood disorders, constipation, and hyposmia. It is expected that besides the regenerative effects of PMSC, the secretion of trophic factors, their anti-inflammatory and antiapoptotic effects, could also alleviate these nonmotor symptoms.

2.3.2. Alzheimer's disease

Alzheimer's disease (AD) pathogenesis is characterized by a deposition of β-amyloid peptide and hyperphosphorylation of tau causing loss of the synaptic and neuronal activities and neuroinflammation. It has been demonstrated that PMSC, transplanted into an Alzheimer's disease mouse model, modulated the inflammatory response. Moreover, mice injected with PMSC presented higher levels of β-amyloid degrading enzymes, reduced levels of pro-inflammatory cytokines, and increased levels of anti-inflammatory cytokines (TGF-β and IL-10). The effect of PMSC injection resulted in an improvement of memory function [70].

2.3.3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by loss of nerve cells in the brain and spinal cord, leading to muscle weakness, paralysis, respiratory problems, and eventually, death. Multiple intravenous injections of PMSC in a mouse model of ALS, resulted in a protection of motor neurons from inflammatory effectors delaying functional deterioration and increasing lifespan [71].

2.3.4. Multiple sclerosis

Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by demyelinated areas in the brain and spinal cord that heal forming a glial scar (sclerosis). It is believed that MS is caused by T cell-mediated autoimmune reaction against proteins of the myelin sheath inducing oligodendrocytes and neuronal loss. Most of therapies in MS patients target the immune system or the inflammatory process. Since the pathogenic process of MS can be divided into inflammatory and degenerative phases, PMSC-based cell therapy seems appropriate since it may be able to specifically regulate immune responses and also induce neuronal regeneration. The animal model that closely resembles the MS symptoms is the experimental autoimmune encephalomyelitis (EAE) in mice where the animals are injected with myelin antigens that initiate an immune response. Several preclinical trials based on the treatment of EAE animals with PMSC have been published. Intracerebroventricular (ICV) transplantation of PMSC at day 5 (pre-symptomatology) or day 14 (at the beginning of the disease) after immunization, significantly reduced the severity of the disease and prolonged survival without delaying the onset of the disease [72]. Several intraperitoneal injections of PMSC in EAE mice delayed the onset of the symptoms and decreased disease incidence in the treated group respect to control, as well as inhibiting T cell proliferation and downregulating the production of pro-inflammatory factors while increasing the production of anti-inflammatory cytokines [73]. Likewise, ICV or intrathecal (ITH) injection of PMSC in EAE rats, also delayed the onset of motor symptoms, reduced inflammation, prevented axonal loss, and reduced disease severity [74].

2.4. Use of placental mesenchymal stem/stromal cells in bone and cartilage diseases

Bone regeneration is the physiological process of bone formation, which is involved in continuous remodeling throughout adult life, and can be observed during bone healing after damage. However, there are large lesions created by traumatism, infection, tumor resection or skeletal

abnormalities in which physiological bone regeneration is not sufficient. There are also other conditions, such as osteoporosis, in which regeneration is compromised. PMSC have the potential to differentiate into osteogenic lineage, and seem to be an appropriate therapeutic option for bone regeneration. The use of 3D scaffolds that support cell differentiation and improve engraftment has become habitual in PMSC-mediated bone regeneration therapy. Several published studies confirm that PMSC have potent in vivo bone-forming capacity and may be worthwhile candidates for in vivo bone tissue repair. So, when PMSC were subcutaneously injected into severe combined immunodeficiency (SCID) mice with hydroxyapatite/tricalcium phosphate particles as a vehicle, new bone formation was found throughout all implants [75]. Another study showed that PMSC administered in combination with nanobiphasic calcium phosphate ceramics in a rat model of femur bone defects produced complete healing of the defect in 3 months without evidence of fibrosis [76].

Osteoarthritis (OA) is a degenerative process of the cartilage in joints. There is still no treatment available to improve or reverse the degenerative process and current pharmacological treatments are only palliative. Given the potential of PMSC to differentiate into musculoskeletal lineages including bone and cartilage, MSC have been proposed as an optimal regenerative cellular therapy for degenerative musculoskeletal conditions as OA. There are numerous data that support this hypothesis in preclinical models. PMSC embedded in a collagen I gel and transplanted in a rat model of femoral cartilage defect appeared to cover the tissue defects with soft tissue positive for toluidine blue suggesting in vivo differentiation of transplanted cells [77]. Also PMSC grown on silk fibroin and transplanted into the knee in rabbits with knee osteochondral defects resulted in newly created hyaline cartilage without inflammatory response [78]. Similarly, PMSC seeded onto poly lactic-co-glycolic acid (PLGA) and preconditioned in chondrogenic medium were well tolerated and found in the reparative tissue of OA rabbit knees 8 weeks after transplantation [79].

2.5. Use of placental mesenchymal stem/stromal cells in liver diseases

Cirrhosis is the common end-stage of most of the injuries affecting the liver such as virus infections, chronic alcoholism, metabolic diseases, or acute liver failure. A scar is formed by extracellular matrix, making the normal function of the liver difficult. Cirrhosis is an irreversible state that can become life-threatening and, frequently, liver transplantation is the only alternative for healing. Donor shortage and continuous need for immunosuppression are the main limitations to liver transplant and cell transplantation appears as a suitable alternative. In addition to fetal and adult hepatocytes, stem cells are considered for cell transplantation. PMSC can be helpful since their potential capacity to differentiate to hepatic-like cells and form functional three-dimensional structures have been reported [80].

Transplanted into animal models of disease, PMSC induced a significant reduction of fibrosis and of serum levels of transaminases. Liver regeneration has been proposed to be promoted by the induction of autophagy process [81], stimulation of liver cell proliferation [82], decreased apoptosis, and suppression of stellate cells activation [83]. Although no evidence of differentiation of the transplanted cells into hepatocytes was reported in a CCl4-induced fibrosis rat model [82], in other models, PMSC engraftment and expression of human albumin and α-fetoprotein have been reported [83–85].

2.6. Use of placental mesenchymal stem/stromal cells in intestinal inflammatory diseases

Crohn's disease (CD) and ulcerative colitis (UC) are chronic conditions caused by a sustained inflammation of the intestinal epithelium that ends in tissue destruction throughout the gastrointestinal tract. It is believed that these disorders are the result of an abnormal host immune response to intraluminal antigens in genetically predisposed individuals. Several genetic variants of nucleotide-binding oligomerization domain 2 (NOD2) are associated with the development of Crohn's disease [86]. Both pathologies have a major impact on the quality of life and there is no curative treatment. Furthermore, many patients are not responsive to current therapy.

Intraperitoneal administration of conditioned medium from PMSC ameliorated clinical parameters in a mouse model of dextran sulfate sodium (DSS)-induced colitis [87]. Intraperitoneal injection of PMSC also prevented the loss of body weight and decreased the mortality of mice. These benefits were greater when NOD2-activated PMSC were used [88].

2.7. Use of placental mesenchymal stem/stromal cells in urological diseases

Stress urinary incontinence (SUI) is a widespread disorder, commonly associated with childbirth, with a detrimental impact on the quality of life. SUI triggers a weakening of muscles and ligaments causing involuntary leakage of urine during physical activity, sneezing, or coughing. Surgical intervention to place a tissue sling that provides support to the urethra is the usual therapeutic action.

Animal models of SUI have been employed to prove the benefits of cell therapy in this pathology. Periurethral injection of myogenic differentiated PMSC in SUI mice restored the urethral sphincter to apparently normal histology and function [89].

3. Use of placenta mesenchymal stem/stromal cells (PMSC) and nanotechnology for tissue regeneration

The goal of cell-based regenerative medicine is to repair, replace, or regenerate cells, tissues, or organs when damaged. However, there are still some unresolved issues such as engraftment of transplanted cells onto the injured tissue and the survival for the time needed to repair the damage. Nanotechnology can be very helpful since nanomaterials can be used as scaffolds to improve the engraftment of stem cells onto the damaged tissue. In addition, the use of nanoparticles (NPs) for gene/drug delivery can complement the therapeutic benefits of transplanted stem cells, and allow the tracking of the cells inside the body [90].

Several reports described the therapeutic application of PMSC combined with biomaterials. PMSC proliferation and differentiation into myocardial and neuronal cells improved when the cells were grown on top of gold-coated collagen nanofibers (GCNFs) [91]. The peptide hydrogel PuraMatrix® (PM; 3-D Matrix, Ltd) was used to support PMSC in rat models of both acute MI and post-MI ischemic cardiomyopathy. The peptide hydrogel and the PMSC create a film to coat the heart. The epicardial "coating" method has advantages with respect to intramyocardial injection such as higher survival of the transplanted cells and lower complications [92].

http://dx.doi.org/10.5772/intechopen.76718

In bone regenerative medicine, the RKKP glass ceramic has been proposed as a biocompatible support for PMSC. RKKP exhibits a higher osteointegration rate compared to other ceramic materials mainly in osteopenic bone. Additionally, the biology of PMSC is not affected when grown over this support while maintaining their osteogenic potential [93] PMSC seeded over poly-L-lactic acid (PLLA) nanofibrous scaffolds and subjected to osteogenic conditions have been successfully grafted in a rabbit model of sternal defect closure [94].

Some systems have shown suitable behaviors as recipients of PMSC for cartilage regeneration. Collagen sponge allowed the formation of a cartilage-like tissue both, in vitro and in vivo, under chondrogenic-inducing conditions [95]. Similarly, PMSC embedded in alginate incorporating nanosized calcium-deficient hydroxyapatite (nCDHA) and/or a recombinant protein containing arginine-glycine-aspartate (RGD) and seeded over poly(D,L-lactide-co-glycolide) (PLGA) gave rise to cartilage formation [96].

The use of nanoparticles for gene/drug delivery can significantly contribute to the advance of regenerative medicine. The use of stem cells as carriers of NPs containing biologically active molecules (e.g., pro-survival, anti-inflammatory) or chemicals such as anticancer drugs is very promising. PMSC have been employed as a platform to load mesoporous silica nanoparticles. NP loading did not affect the chemotactic ability of PMSC toward tumors in vitro and in vivo. When carrying doxorubicin-loaded NP, PMSC promoted breast cancer cells death in a co-culture system [97]. In a proof of concept, ultrasound-responsive NPs loaded with antitumor drugs were transported to tumor tissues by PMSC, and the cargo was released by NPs only after ultrasound application [98].

In vivo monitoring of cells, after transplant, is needed and NP-based probes are useful for this purpose. They offer the possibility of tracking the bio-distribution and engraftment of cells into the body with minimally invasive techniques. However these probes have to ensure minimal changes in cell phenotype [97]. PMSC have been efficiently labeled with albumin-conjugated fluorescent nanodiamonds (FNDs) [99], with silica-coated magnetic nanoparticles incorporating rhodamine B isothiocyanate, MNPs@SiO2(RITC) [100], with rhodamine B labeled mesoporous silica nanoparticles [98] and with human serum albumin coated iron oxide nanoparticles (HSA-IONPs) [101] without any detrimental effect.

4. Therapeutic applications of placenta mesenchymal stem/stromal cells (PMSC) in clinical trials

Based on the benefits produced by transplanted PMSC in different animal models resembling human diseases, some clinical studies have been carried out and there are also an increasing number of ongoing clinical trials. The web pages http://www.clinicaltrialsregister.eu and http://www.clinicaltrial.gov offer up-to-date information on clinical trials giving current status. There are a good number of completed trials of which no results have yet been published. Other completed studies and clinical trials have published reports with the results obtained demonstrating the safety of the use of PMSC. In general, therapeutic benefits have been found.

Intracoronary infusion of UC-MSC in MI patients resulted in safe and significantly improved myocardial viability and the perfusion within the infarcted area. Improvement in some

parameters such as the increase in the left ventricular ejection fraction (LVEF) and decreases in end-diastolic volumes and LV end-systolic volumes were observed up to 18 months after treatment [102]. RIMECARD is a phase I/II clinical trial that has demonstrated the safety and efficacy of the intravenous infusion of UC-MSC in patients with chronic heart failure and reduced ejection fraction. Improvements in left ventricular function, functional status, and the quality of life were observed in treated subjects [103].

Cell therapy has been introduced as a new therapeutic attempt to restore blood flow and attenuate ischemia promoting collateral vessel formation in CLI. In January 2017, a Phase III study of PLX-PAD cells[1] in the treatment of critical limb ischemia (CLI) has been cleared by the U.S. Food and Drug Administration (FDA). Data from previous studies have shown that by increasing tissue perfusion, PMSC may improve the healing of wounds in CLI patients, and could allow for significant delays in events of amputation and death.

Safety and efficacy of UC-MSC infusion in patients with decompensated liver cirrhosis have been reported in a 1-year follow-up study. There were no significant side effects or complications and there was a significant reduction in the volume of ascites and improvement in liver function, as indicated by the increase of serum albumin levels and a decrease in total serum bilirubin levels [104].

Therapeutic effects of PMSC transplantation in MS patients have been evaluated in different studies. Intravenous infusion of UC-MSC appears to be safe and well tolerated in patients with MS, and the overall symptoms of treated patients remained stable or improved compared to the control group [105]. In another clinical trial, patients with relapsing-remitting MS or with secondary progressive MS randomly received PMSC (PDA-001)[2] and most treated subjects had stable or decreasing Expanded Disability Status Scale scores [106].

OA affecting the hip can mean, in many cases, the need for a total hip replacement (THR). A frequent side effect of THR is a gluteus medius injury. PMSC administered directly to the injured muscle during surgery have demonstrated their safety and efficacy inducing a greater increase in the gluteus medius muscle strength than placebo, and a significant improvement in muscle volume based on MRI. EudraCT Number: 2011-003934-16.

Safety of the intravenous administration of PMSC (PDA001) to moderate-to-severe Crohn's disease patients unresponsive to other therapies has been demonstrated and some remission rates of the disease have been reported [107]. Likewise, in a randomized controlled clinical trial, intravenous injection of PMSC patient condition improved significantly allowing a significant reduction in steroid dosage. Additionally, several patients with anal fistula showed remarkable improvement [108].

[1] PLX-PAD – Placenta eXpanded adherent stromal cells produced by PluriStem Ltd. PLX-PAD cells are derived from the decidua of human placenta and are expanded using the company's 3D proprietary technology.

[2] PDA-001 (previously cenplacel-L) is a placenta adherent cells-based therapy developed by Celgene Cellular Therapeutics (CCT, a subsidiary of Celgene Corporation) to treat autoimmune diseases. It is administered as an intravenous injection.

http://dx.doi.org/10.5772/intechopen.76718

5. Conclusions

PMSC are promising candidates for use in regenerative medicine in humans. Cell therapy using PMSC is based mostly on three important characteristics of these types of cells: (i) their inherent reparative capacities or by secretion of paracrine factors; (ii) their homing and engraftment abilities; and (iii) their immune modulation capacities. However, clinical use of PMSC is still in its infancy and most of the trials are, to date, under development. Most studies of cellular therapy have been realized with autologous cells. Nevertheless, the use of patient's own cells has several limitations. First, there is a time-limiting factor as the expansion and quality control of autologous cells may require several weeks. Furthermore, the cells can show less potency due to inherent aging aspects and, even, certain characteristics of the subject may render autologous transplantation unfeasible as occurs in the case of elderly patients and those having a specific systemic disease such as diabetes. In contrast, allogeneic MSC have the potential to be mass-produced rapidly so they can be readily available and administered immediately. They can be obtained under more standardized and strictly validated conditions and probably reduce costs. To date, published data regarding reliability of treatment with PMSC indicate that the use of PMSC is safe and therefore there are already products "off-the-shelf." Although most clinical trials are ongoing or have no published results, there are some favorable data regarding to the efficacy of treatments with PMSC.

Stem cell nanomedicine is a very promising field that at the preclinical level has yielded very encouraging results. Treatment of certain pathologies can benefit from the use of scaffolds that provide a three-dimensional structure to give support to the cells, promoting their adhesion and growth, so definitely improving the engraftment and therefore the therapeutic results. Besides the use of cells as carriers of nanoparticles to deliver drugs inside the injured tissue and, even more, the possibility of stimulus-controlled release of the drug appears exciting.

Acknowledgements

This work was funded by project PI15/01803 [Instituto de Salud Carlos III (Ministry of Economy, Industry and Competitiveness) and cofunded by the European Regional Development Fund]; and by project Multimat Challenge (S2013/MIT-2862-CM, funded by the Regional Government of Madrid and EU Structural Funds), and approved by the Ethics Committee of our Institution.

The authors are very grateful to Ian Ure for proofreading the English version of this chapter.

Conflict of interest

The authors declare no conflict of interest.

Author details

Paz de la Torre, María Jesús Pérez-Lorenzo and Ana I. Flores*

*Address all correspondence to: anaisabel.flores@salud.madrid.org

Regenerative Medicine Group, Research Centre, Research Institute of Hospital 12 de Octubre (imas12), Madrid, Spain

References

[1] Cross JC, Werb Z, Fisher SJ. Implantation and the placenta: Key pieces of the development puzzle. Science. 1994;**266**(5190):1508-1518

[2] Siiteri PK, Stites DP. Immunologic and endocrine interrelationships in pregnancy. Biology of Reproduction. 1982;**26**(1):1-14

[3] Cunningham F, Leveno KJ, Bloom S, Hauth J, Gilstrap L, Wenstrom K, Capítulo 3: Implantación, Embriogénesis y desarrollo placentario. In: Obstetricia de Williams. 22nd ed. México: Mc Graw Hill; 2006. pp. 39-83

[4] Pijnenborg R et al. Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy. Placenta. 1980;**1**(1):3-19

[5] Timiras PS. Development and plasticity of the nervous system. In: Timiras PS, editor. Developmental Physiology and Aging. New York: Macmillan; 1972. pp. 129-165

[6] Burton GJ, Watson AL. The structure of the human placenta: Implications for initiating and defending against virus infections. Reviews in Medical Virology. 1997;**7**(4):219-228

[7] Yen BL et al. Isolation of multipotent cells from human term placenta. Stem Cells. 2005; **23**(1):3-9

[8] Shigeno Y, Ashton BA. Human bone-cell proliferation in vitro decreases with human donor age. Journal of Bone and Joint Surgery. British Volume (London). 1995;**77**(1):139-142

[9] Macias MI et al. Isolation and characterization of true mesenchymal stem cells derived from human term decidua capable of multilineage differentiation into all 3 embryonic layers. American Journal of Obstetrics & Gynecology. 2010;**203**(5):495 e9-495 e23

[10] Medawar PB. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. Symposia of the Society for Experimental Biology. 1953; **7**:320-338

[11] Bailo M et al. Engraftment potential of human amnion and chorion cells derived from term placenta. Transplantation. 2004;**78**(10):1439-1448

[12] Vegh I et al. Decidua mesenchymal stem cells migrated toward mammary tumors in vitro and in vivo affecting tumor growth and tumor development. Cancer Gene Therapy. 2013; **20**(1):8-16

[13] Kurtzberg J et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. The New England Journal of Medicine. 1996;**335**(3):157-166

[14] Gnecchi M et al. Paracrine mechanisms in adult stem cell signaling and therapy. Circulation Research. 2008;**103**(11):1204-1219

[15] Lee JM et al. Comparison of immunomodulatory effects of placenta mesenchymal stem cells with bone marrow and adipose mesenchymal stem cells. International Immunopharmacology. 2012;**13**(2):219-224

[16] Murphy SP, Choi JC, Holtz R. Regulation of major histocompatibility complex class II gene expression in trophoblast cells. Reproductive Biology and Endocrinology. 2004;**2**:52

[17] Carosella ED, Dausset J, Rouas-Freiss N. Immunotolerant functions of HLA-G. Cellular and Molecular Life Sciences. 1999;**55**(3):327-333

[18] Le Bouteiller P et al. Placental HLA-G protein expression in vivo: Where and what for? Human Reproduction Update. 1999;**5**(3):223-233

[19] McCracken SA et al. NF-kappaB-regulated suppression of T-bet in T cells represses Th1 immune responses in pregnancy. European Journal of Immunology. 2007;**37**(5):1386-1396

[20] Bowen JM et al. Cytokines of the placenta and extra-placental membranes: Biosynthesis, secretion and roles in establishment of pregnancy in women. Placenta. 2002;**23**(4):239-256

[21] Heikkinen J et al. Phenotypic characterization of regulatory T cells in the human decidua. Clinical and Experimental Immunology. 2004;**136**(2):373-378

[22] Christensen JL et al. Circulation and chemotaxis of fetal hematopoietic stem cells. PLoS Biology. 2004;**2**(3):E75

[23] Miki T et al. Stem cell characteristics of amniotic epithelial cells. Stem Cells. 2005; **23**(10):1549-1559

[24] Li H et al. Immunosuppressive factors secreted by human amniotic epithelial cells. Investigative Ophthalmology & Visual Science. 2005;**46**(3):900-907

[25] Takao T et al. Isolation and characterization of human trophoblast side-population (SP) cells in primary villous cytotrophoblasts and HTR-8/SVneo cell line. PLoS One. 2011;**6**(7):e21990

[26] Ringler GE, Strauss JF 3rd. In vitro systems for the study of human placental endocrine function. Endocrine Reviews. 1990;**11**(1):105-123

[27] Igura K et al. Isolation and characterization of mesenchymal progenitor cells from chorionic villi of human placenta. Cytotherapy. 2004;**6**(6):543-553

[28] Soncini M et al. Isolation and characterization of mesenchymal cells from human fetal membranes. Journal of Tissue Engineering and Regenerative Medicine. 2007;**1**(4):296-305

[29] Wang HS et al. Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord. Stem Cells. 2004;**22**(7):1330-1337

[30] Dominici M et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;**8**(4):315-317

[31] Parolini O et al. Concise review: Isolation and characterization of cells from human term placenta: Outcome of the first international workshop on placenta derived stem cells. Stem Cells. 2008;**26**(2):300-311

[32] Prusa AR, Hengstschlager M. Amniotic fluid cells and human stem cell research: A new connection. Medical Science Monitor. 2002;**8**(11):RA253-RA257

[33] De Coppi P et al. Isolation of amniotic stem cell lines with potential for therapy. Nature Biotechnology. 2007;**25**(1):100-106

[34] Owen M. Marrow stromal stem cells. Journal of Cell Science. Supplement. 1988;**10**:63-76

[35] Friedenstein AJ et al. Precursors for fibroblasts in different populations of hematopoietic cells as detected by the in vitro colony assay method. Experimental Hematology. 1974;**2**(2):83-92

[36] Moodley Y et al. Anti-inflammatory effects of adult stem cells in sustained lung injury: A comparative study. PLoS One. 2013;**8**(8):e69299

[37] Bonomi A et al. Human amniotic mesenchymal stromal cells (hAMSCs) as potential vehicles for drug delivery in cancer therapy: An in vitro study. Stem Cell Research & Therapy. 2015;**6**:155

[38] Chen L et al. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. PLoS One. 2008;**3**(4):e1886

[39] Macias MI et al. Isolation and characterization of true mesenchymal stem cells derived from human term decidua capable of multilineage differentiation into all 3 embryonic layers. American Journal of Obstetrics and Gynecology. 2010;**203**(5):495.e9-495.e23

[40] Barlow S et al. Comparison of human placenta- and bone marrow-derived multipotent mesenchymal stem cells. Stem Cells and Development. 2008;**17**(6):1095-1107

[41] Wagner W et al. Aging and replicative senescence have related effects on human stem and progenitor cells. PLoS One. 2009;**4**(6):e5846

[42] Bork S et al. DNA methylation pattern changes upon long-term culture and aging of human mesenchymal stromal cells. Aging Cell. 2010;**9**(1):54-63

[43] Brandl A et al. Oxidative stress induces senescence in human mesenchymal stem cells. Experimental Cell Research. 2011;**317**(11):1541-1547

[44] Ruster B et al. Mesenchymal stem cells display coordinated rolling and adhesion behavior on endothelial cells. Blood. 2006;**108**(12):3938-3944

[45] Karlsson H et al. Stromal cells from term fetal membrane are highly suppressive in allogeneic settings in vitro. Clinical and Experimental Immunology. 2012;**167**(3):543-555

[46] Abumaree MH et al. Human placental mesenchymal stem cells (pMSCs) play a role as immune suppressive cells by shifting macrophage differentiation from inflammatory M1 to anti-inflammatory M2 macrophages. Stem Cell Reviews. 2013;**9**(5):620-641

[47] Yust-Katz S et al. Placental mesenchymal stromal cells induced into neurotrophic factor-producing cells protect neuronal cells from hypoxia and oxidative stress. Cytotherapy. 2012;**14**(1):45-55

[48] Zhao P et al. Human amniotic mesenchymal cells have some characteristics of cardiomyocytes. Transplantation. 2005;**79**(5):528-535

[49] Okamoto K et al. 'Working' cardiomyocytes exhibiting plateau action potentials from human placenta-derived extraembryonic mesodermal cells. Experimental Cell Research. 2007;**313**(12):2550-2562

[50] Li L et al. Hypoxia modulates cell migration and proliferation in placenta-derived mesenchymal stem cells. The Journal of Thoracic and Cardiovascular Surgery. 2017;**154**(2):543-552 e3

[51] Lopez Y et al. Wharton's jelly or bone marrow mesenchymal stromal cells improve cardiac function following myocardial infarction for more than 32 weeks in a rat model: A preliminary report. Current Stem Cell Research & Therapy. 2013;**8**(1):46-59

[52] Simioniuc A et al. Placental stem cells pre-treated with a hyaluronan mixed ester of butyric and retinoic acid to cure infarcted pig hearts: A multimodal study. Cardiovascular Research. 2011;**90**(3):546-556

[53] Danieli P et al. Conditioned medium from human amniotic mesenchymal stromal cells limits infarct size and enhances angiogenesis. Stem Cells Translational Medicine. 2015;**4**(5):448-458

[54] Prather WR et al. The role of placental-derived adherent stromal cell (PLX-PAD) in the treatment of critical limb ischemia. Cytotherapy. 2009;**11**(4):427-434

[55] Kim HG, Choi OH. Neovascularization in a mouse model via stem cells derived from human fetal amniotic membranes. Heart and Vessels. 2011;**26**(2):196-205

[56] Xie N et al. Transplantation of placenta-derived mesenchymal stem cells enhances angiogenesis after ischemic limb injury in mice. Journal of Cellular and Molecular Medicine. 2016;**20**(1):29-37

[57] Liang L et al. Transplantation of Human Placenta-Derived Mesenchymal Stem Cells Alleviates Critical Limb Ischemia in Diabetic Nude Rats. Cell Transplant. 2017;**26**(1):45-61

[58] Zahavi-Goldstein E et al. Placenta-derived PLX-PAD mesenchymal-like stromal cells are efficacious in rescuing blood flow in hind limb ischemia mouse model by a dose- and site-dependent mechanism of action. Cytotherapy. 2017;**19**(12):1438-1446

[59] Chen J et al. Neuroprotective effect of human placenta-derived cell treatment of stroke in rats. Cell Transplantation. 2013;**22**(5):871-879

[60] Dvorak HF. Tumors: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. The New England Journal of Medicine. 1986;**315**(26):1650-1659

[61] Spaeth E et al. Inflammation and tumor microenvironments: Defining the migratory itinerary of mesenchymal stem cells. Gene Therapy. 2008;**15**(10):730-738

[62] Silini AR et al. The dichotomy of placenta-derived cells in cancer growth. Placenta. 2017;**59**:154-162

[63] Allen H et al. Human placental-derived adherent stromal cells co-induced with TNF-alpha and IFN-gamma inhibit triple-negative breast cancer in nude mouse Xenograft models. Scientific Reports. 2018;**8**(1):670

[64] Chen Q et al. Antitumor activity of placenta-derived mesenchymal stem cells producing pigment epithelium-derived factor in a mouse melanoma model. Oncology Letters. 2012;**4**(3):413-418

[65] Zheng L et al. Antitumor activities of human placenta-derived mesenchymal stem cells expressing endostatin on ovarian cancer. PLoS One. 2012;**7**(7):e39119

[66] Portmann-Lanz CB, et al. Turning placenta into brain: placental mesenchymal stem cells differentiate into neurons and oligodendrocytes. American Journal of Obstetrics & Gynecology. 2010;**202**(3):294 e1-294 e11

[67] Martini MM et al. Human placenta-derived mesenchymal stem cells acquire neural phenotype under the appropriate niche conditions. DNA and Cell Biology. 2013;**32**(2):58-65

[68] Chen L, He DM, Zhang Y. The differentiation of human placenta-derived mesenchymal stem cells into dopaminergic cells in vitro. Cellular & Molecular Biology Letters. 2009;**14**(3):528-536

[69] Park S et al. Dopaminergic differentiation of neural progenitors derived from placental mesenchymal stem cells in the brains of Parkinson's disease model rats and alleviation of asymmetric rotational behavior. Brain Research. 2012;**1466**:158-166

[70] Kim KS et al. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. Neurobiology of Aging. 2013;**34**(10):2408-2420

[71] Garbuzova-Davis S et al. Multiple intravenous administrations of human umbilical cord blood cells benefit in a mouse model of ALS. PLoS One. 2012;**7**(2):e31254

[72] Fisher-Shoval Y et al. Transplantation of placenta-derived mesenchymal stem cells in the EAE mouse model of MS. Journal of Molecular Neuroscience. 2012;**48**(1):176-184

[73] Bravo B et al. Restrained Th17 response and myeloid cell infiltration into the central nervous system by human decidua-derived mesenchymal stem cells during experimental autoimmune encephalomyelitis. Stem Cell Research & Therapy. 2016;**7**:43

[74] Jiang H et al. Amelioration of experimental autoimmune encephalomyelitis through transplantation of placental derived mesenchymal stem cells. Scientific Reports. 2017;**7**:41837

[75] Kusuma GD et al. Ectopic bone formation by mesenchymal stem cells derived from human term placenta and the decidua. PLoS One. 2015;**10**(10):e0141246

[76] Reddy S et al. Evaluation of nano-biphasic calcium phosphate ceramics for bone tissue engineering applications: In vitro and preliminary in vivo studies. Journal of Biomaterials Applications. 2013;**27**(5):565-575

[77] Wei JP et al. Human amniotic mesenchymal cells differentiate into chondrocytes. Cloning and Stem Cells. 2009;**11**(1):19-26

[78] Li F et al. Human placenta-derived mesenchymal stem cells with silk fibroin biomaterial in the repair of articular cartilage defects. Cellular Reprogramming. 2012;**14**(4):334-341

[79] Nogami M et al. Isolation and characterization of human amniotic mesenchymal stem cells and their chondrogenic differentiation. Transplantation. 2012;**93**(12):1221-1228

[80] Bornstein R et al. Human decidua-derived mesenchymal stromal cells differentiate into hepatic-like cells and form functional three-dimensional structures. Cytotherapy. 2012;**14**(10):1182-1192

[81] Jung J et al. Human placenta-derived mesenchymal stem cells promote hepatic regeneration in CCl4 -injured rat liver model via increased autophagic mechanism. Stem Cells. 2013;**31**(8):1584-1596

[82] Tsai PC et al. The therapeutic potential of human umbilical mesenchymal stem cells from Wharton's jelly in the treatment of rat liver fibrosis. Liver Transplantation. 2009; **15**(5):484-495

[83] Zhang D, Jiang M, Miao D. Transplanted human amniotic membrane-derived mesenchymal stem cells ameliorate carbon tetrachloride-induced liver cirrhosis in mouse. PLoS One. 2011;**6**(2):e16789

[84] Cao H et al. Therapeutic potential of transplanted placental mesenchymal stem cells in treating Chinese miniature pigs with acute liver failure. BMC Medicine. 2012;**10**:56

[85] Yu J et al. Therapeutic effect and location of GFP-Labeled placental mesenchymal stem cells on hepatic fibrosis in rats. Stem Cells International. 2017;**2017**:1798260

[86] Hugot JP et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001;**411**(6837):599-603

[87] Song JY et al. Umbilical cord-derived mesenchymal stem cell extracts reduce colitis in mice by re-polarizing intestinal macrophages. Scientific Reports. 2017;**7**(1):9412

[88] Kim HS et al. Human umbilical cord blood mesenchymal stem cells reduce colitis in mice by activating NOD2 signaling to COX2. Gastroenterology. 2013;**145**(6):1392-403 e1-1392-403 e8

[89] Kim BS et al. Human amniotic fluid stem cell injection therapy for urethral sphincter regeneration in an animal model. BMC Medicine. 2012;**10**:94

[90] Hofmann MC. Stem cells and nanomaterials. Advances in Experimental Medicine and Biology. 2014;**811**:255-275

[91] Orza A et al. Electrically conductive gold-coated collagen nanofibers for placental-derived mesenchymal stem cells enhanced differentiation and proliferation. ACS Nano. 2011;**5**(6):4490-4503

[92] Ichihara Y et al. Self-assembling peptide hydrogel enables instant epicardial coating of the heart with mesenchymal stromal cells for the treatment of heart failure. Biomaterials. 2018;**154**:12-23

[93] Ledda M et al. Placenta derived mesenchymal stem cells hosted on RKKP glass-ceramic: A tissue engineering strategy for bone regenerative medicine applications. BioMed Research International. 2016;**2016**:3657906

[94] Steigman SA et al. Sternal repair with bone grafts engineered from amniotic mesenchymal stem cells. Journal of Pediatric Surgery. 2009;**44**(6):1120-6; discussion 1126

[95] Liu D et al. Construction of tissue-engineered cartilage using human placenta-derived stem cells. Science China. Life Sciences. 2010;**53**(2):207-214

[96] Hsu SH et al. Chondrogenesis from human placenta-derived mesenchymal stem cells in three-dimensional scaffolds for cartilage tissue engineering. Tissue Engineering. Part A. 2011;**17**(11-12):1549-1560

[97] Paris JL et al. Decidua-derived mesenchymal stem cells as carriers of mesoporous silica nanoparticles. In vitro and in vivo evaluation on mammary tumors. Acta Biomaterialia. 2016;**33**:275-282

[98] Paris JL et al. Vectorization of ultrasound-responsive nanoparticles in placental mesenchymal stem cells for cancer therapy. Nanoscale. 2017;**9**(17):5528-5537

[99] Su LJ et al. Fluorescent nanodiamonds enable quantitative tracking of human mesenchymal stem cells in miniature pigs. Scientific Reports. 2017;**7**:45607

[100] Park KS et al. Characterization, in vitro cytotoxicity assessment, and in vivo visualization of multimodal, RITC-labeled, silica-coated magnetic nanoparticles for labeling human cord blood-derived mesenchymal stem cells. Nanomedicine. 2010;**6**(2):263-276

[101] Sanganeria P et al. Effect of HSA coated iron oxide labeling on human umbilical cord derived mesenchymal stem cells. Nanotechnology. 2015;**26**(12):125103

[102] Gao LR et al. Intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells in acute myocardial infarction: Double-blind, randomized controlled trial. BMC Medicine. 2015;**13**:162

[103] Bartolucci J et al. Safety and efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure: A phase 1/2 randomized controlled trial (RIMECARD trial [randomized clinical trial of intravenous infusion umbilical cord mesenchymal stem cells on cardiopathy]). Circulation Research. 2017;**121**(10):1192-1204

[104] Zhang Z et al. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. Journal of Gastroenterology. 2012;**27**(Suppl 2):112-120

[105] Li JF et al. The potential of human umbilical cord-derived mesenchymal stem cells as a novel cellular therapy for multiple sclerosis. Cell Transplant. 2014;**23**(Suppl 1):S113-S122

[106] Lublin FD et al. Human placenta-derived cells (PDA-001) for the treatment of adults with multiple sclerosis: A randomized, placebo-controlled, multiple-dose study. Multiple Sclerosis and Related Disorders. 2014;**3**(6):696-704

[107] Mayer L et al. Safety and tolerability of human placenta-derived cells (PDA001) in treatment-resistant crohn's disease: A phase 1 study. Inflammatory Bowel Diseases. 2013;**19**(4):754-760

[108] Zhang J et al. Umbilical cord mesenchymal stem cell treatment for Crohn's disease: A randomized controlled clinical trial. Gut and Liver. 2018;**12**(1):73-78

IntechOpen