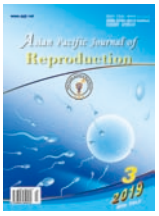

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Human umbilical cord-derived mesenchymal stem cells: Current trends and future perspectives

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ABSTRACT

Among resources of mesenchymal stem cells, human umbilical cord appears to be a rising source capable of differentiating into all germ layers, reaching and repairing lesion areas, and promoting wound repair, and it has also the capacity to influence the immune response. Human umbilical cord-derived mesenchymal stem cells are considered to be an optimal resource compared with other mesenchymal stem cells sources because they require a non-invasive recovery. All these characteristics allow their use in heterogeneous applications. Human umbilical cord-derived mesenchymal stem cells can regenerate tissues, stimulate angiogenesis, modulate inflammatory pathway signals and recruit endogenous stem cell. Human umbilical cord-derived mesenchymal stem cells suppress mitogen-induced signals and modulate the activation and proliferation of several immune cells, modifying lymphocyte phenotypes activity. In culture, human umbilical cord-derived mesenchymal stem cellss show the capacity to create several tissues such as bone, cartilage, and fat. Human umbilical cord-derived mesenchymal stem cells can be isolated from the different compartments of umbilical cord and processed by using different techniques. Clinical applications of human umbilical cord-derived mesenchymal stem cells include graft-*versus*-host disease, autoimmune diseases such as Sjögren's syndrome and diabetes mellitus types 1 and 2, gynecological disorders like endometriosis. Recent studies have shown possible application on rheumatoid arthritis, osteoarthritis, and neuronal degenerative diseases. This review is focused on the resources, molecular profiles, propriety, *in vitro* characterizations, clinical applications and possible future usage of human umbilical cord-derived mesenchymal stem cells.

1. Introduction

Mesenchymal stem cells (MSCs) possess characteristics of multipotent cells. Considering stem cells and mesenchymal progenitors of cells, they can differentiate into several tissues. Stem cells are able to self-renew, and at the same time, by asymmetric cell division or after specific activation, to generate lineage progenitor cells or differentiated cells. MSCs can be found in different human tissues such as fat, umbilical cord (UC), skin, placenta, amniotic

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fluid, synovial membranes, muscle and fetal tissues[1-5]. Due to their immunomodulatory properties and potential for tissue regeneration, they can be used therapeutically, especially for autoimmune and degenerative diseases.

UC, a fetal-placental unit component, is composed of vessels (two arteries and one vein) surrounded by a specific mesenchymal tissue named Wharton's jelly. Among UC components, there are MSCs that demonstrate similar characteristic to other MSC sources. Human umbilical cord-derived mesenchymal stem cells (UC-MSCs) are an optimal resource compared with others, as MSCs require non-invasive recovery and they are a source of a good amount of MSCs. Moreover, they are not compounded by ethical problems and can be used for heterogeneous application[6,7]. For this reason, the aim of our systematic review is to discuss characteristics, the isolation methods and *in vitro* and *in vivo* studies and applications of UC-MSCs.

2. Materials and methods

2.1. Search and screening of literature

We searched the following electronic bibliographic databases: MEDLINE, EMBASE, PsycINFO, Global Health, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register), Health Technology Assessment Database, and Web of Science (science and social science citation index). The search strategy included only terms relating to or describing the intervention, adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials (where these are available): "human umbilical cord stem cells"; "isolation of cord stem cells"; "immunomodulation of human umbilical cord stem cells"; "tissue regenerative properties of human umbilical cord stem cells"; and "human umbilical cord stem cells therapies". The search included articles in English language from the inception of the abovementioned databases to 1 April 2019.

2.2. Data extraction

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two review authors (D.R., C.C.) to identify studies that potentially meet the inclusion criteria outlined above. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by two review team members (D.L., C.V.). Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third (external) collaborator. A standardized, pre-piloted form was used to extract data from the included studies for assessment and evidence synthesis. Two review authors extracted data independently (S.D.A.A., T.K.), discrepancies were identified and resolved through discussion (with a third external collaborator where necessary). Missing data were requested from study authors, when required.

2.3. Data synthesis

Considering the range of different outcomes measured across the studies and the very limited number of trials, we provided a narrative synthesis of the findings from the included articles. In particular, we divided these results into subchapters: "history and characteristic of MSCs and UC-MSCs", "isolation and storage of UC-MSCs", "*in vitro* and animal study" and "human protocols".

3. Results

We identified 13 809 articles, using the search strategy as detailed in the "Materials and methods" section, and 875 additional sources. After duplicates removed, we screened the remaining 234 articles: afterwards, we excluded 127 articles (89 were not published in English, 38 did not report detailed information about the topic). We retrieved and evaluate the remaining 107 articles, and further excluded 56 of them since they did not report detailed information about the topic. Data extracted from the remaining 51 studies are synthetized in the next sections. The full search, screening, and selection of the articles was summarized in the flow diagram of preferred reporting items for systematic reviews and meta-analyses (Figure 1).

3.1. History and characteristic of MSCs and UC-MSCs

Since Conheim's first discovery in 1867, concerning the presence of non-hematopoietic stem cells in bone marrow, numerous studies have been published. The stem cells, first observed in bone marrow as plastic-adherent fibroblastic cells capable of creating colonies *in vitro*[8], were named MSCs. They demonstrated the ability to differentiate into a variety of mesodermal cell types *in vitro*, such as osteoblasts, chondrocytes, adipocytes, and myoblasts[2,9,10]. MSCs can be found in several human tissues such as fat sources, dental pulp, tendon, UC, skin, placenta, amniotic fluid, synovial membranes, muscle and fetal tissues[10-16]. The UC, similar to bone marrow, contains a considerable amount of MSCs. The UC-MSCs are easily collected at the time of birth following either normal vaginal delivery or cesarean section and can be used in the heterogeneous application. Their cost is yet considerably less expensive when compared to other invasive procedures such as bone marrow aspiration. Several studies demonstrated that UC-MSCs have a similar surface phenotype, differentiation capability, and immune properties compared to bone marrow and adipose MSCs. UC-MSCs, in particular, have more in common with fetal MSCs in terms of their *in vitro* expansion potential[17]. UC-MSCs have the ability to generate multipotent *in vitro* and adherent cells with osteogenic and chondrogenic potential. There are two different morphological phenotypes: flattened fibroblasts (majority) and spindle-shaped fibroblasts (minority) and they exhibit similar cell surface markers. MSCs are negative for CD34, CD26, CD31, CD73, CD90, CD105, CD44, and human lymphocyte antigen (HLA)-DR. They are positive for mesenchymal progenitor markers SH2, SH3, and SH4; adherent molecules CD29, CD44 and HLA-A, B, C. However,

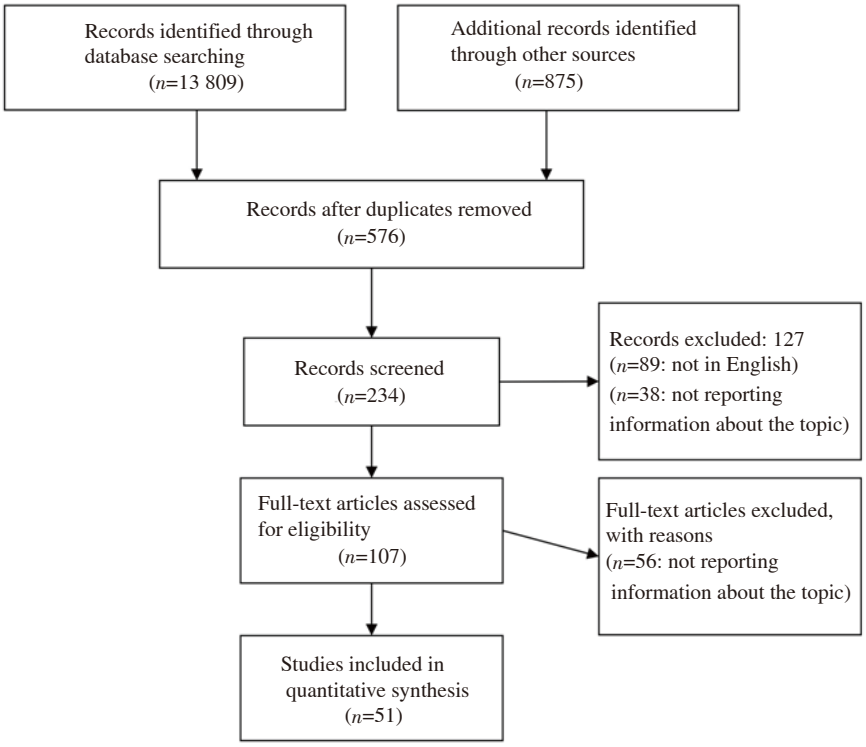

Figure 1. Flow diagram of full search, screening and selection of articles.

a difference in CD90 expression was observed. Both morphological phenotypes of MSCs have shown the ability to differentiate into osteogenic and chondrogenic lines, but the flattened type has shown less capability in terms of differentiation and adipogenesis. This characteristic justifies the lesser sensitivity of UC-MSCs compared with bone marrow MSCs in generating adipogenic tissues[18,19]. Comparative proteomic analysis of bone marrow, placenta and adipose tissue derived from MSCs showed that 90 proteins were expressed differently according to their functional tissue orientation towards chondrogenic, adipogenic or osteogenic differentiation, such as apoptosis, oxidative stress and peroxiredoxin activity, stathmin, transgelin, tropomyosin, and heat shock protein 27. Placenta-derived MSCs, similar to UC-MSCs, have a lower potential for undergoing adipogenesis but have a higher potential for undergoing osteogenesis compared to other MSCs[15]. Due to the presence of highly up-regulated apoptosis, oxidative stress and peroxiredoxin activity proteins, fetal-MSCs seem to be potential in the treatment of cellular ischemic disease caused by hypoxic conditions[20]. UC-MSCs are easily found, manageable and expandable *in vitro*; they can be used in the heterogeneous application, cryogenically stored and reanimated. MSCs must be managed in compliance with good medical practice. Therefore, cells must be tested in accordance with the high standards of sterility protocols, quality control, storage and documentation[21].

3.2. Isolation and storage of UC-MSC

In order to carry out UC-MSC isolation and storage, informed consent should be obtained from each donor-mother prior to delivery. Afterwards, collection is obtained from the UC or explanted from several body compartments. Collected tissue should be then stored in 0.9% saline solution, handled and processed in a sterilized container within 12-24 h after delivery, using phosphate buffered saline in order to remove blood residues. Among the various techniques used to isolate UC-MSCs, we address hereby the most commonly practiced[22].

3.3. Explant method

The first step is to remove blood vessels from the UC and cut them into small parts. Later on, the UC fragments are put into a culture-treated dish where they are attached to the bottom, using a medium replaced every 3.7 days for 2-4 weeks until a high level of fibroblast concentration is obtained. Following this, the UC fragments are detached through a trypsin solution and filtered. As one can imagine, the main limit of this technique is the low rate of retrieved cells due to the gross tissue fragments within the medium[22].

3.4. Enzymatic digestion method

In this method, it is important to remove the blood vessels, cut the UC into small parts of about 4 cm in well-lit conditions with a sterile blade, then mince and digest them with a specific enzyme solution at 37 ℃. Among the different enzymes, the most used are collagenase and hyaluronidase, with or without trypsin. Subsequently, cells are divided into two parts: the first is frozen in liquid nitrogen; the second is cultured with standard conditions and specific culture media. For instance, it is possible to use the alpha minimum essential

culture media supplemented with 2 mmol/L L-glutamine, 100 U penicillin /1 000 U streptomycin and 15% fetal bovine serum[22,23]. The culture medium is changed every 3-7 days for at least 2 weeks until a high level of fibroblast concentration is obtained. After culture, cells are divided into two parts as before: one frozen and the other used for immunophenotypic assays[24]. Cells are counted by an automated cell counter system and the growth rate is calculated through doubling time evaluation. Flow cytometry analysis is usually arranged in the dark for 30 min at room temperature using specific antibodies such as CD105-PerCP-Cy5.5, CD31-phycoerythrin (PE), CD73-allophycocyanin, CD34-PE, PE-CD11b, CD90-fluorescein isothiocyanate, CD44-PE, CD19-PE, PE-CD117, CD146-PE and HLA-DR-PE[22].

3.5. In vitro and animal study

Among MSCs, UC-MSCs show remarkable plasticity, capable of differentiating *in vitro* into different lines of multipotent cells: adipocytes, osteoblasts, myogenic cells, neurons, and cardiomyocytes. They demonstrate a simultaneous immune-privilege due to the lack of HLA-DR and immune-modulatory properties. These characteristics have made UC-MSCs a new clinical tool in the exploration of new medical frontiers in several autoimmune and chronic inflammatory disorders and in the repair of injured tissue[25–30]. Several studies were carried out, both *in vitro* and *in vivo*, to demonstrate the capability of UC-MSCs in modulating the immune system, repopulating and regenerating damaged tissues as well as in producing immunomodulation and immunosuppression function, changing the pathological mechanism of some diseases[24].

UC-MSCs are candidate cells in the treatment of autoimmune diseases thanks to their immunomodulatory properties, for example, their ability to modify systemic lupus erythematosus disease by increasing the frequency of peripheral T-regulatory (Treg) cells and re-establishing the balance between lymphocytes T helper (Th)1- and Th2-related cytokines[25]. Yang *et al* demonstrated that UC-MSCs co-cultured with peripheral blood mononuclear cells are capable of suppressing mitogen-induced peripheral blood mononuclear cell activation and proliferation, modifying T lymphocyte phenotypes *in vitro* and changing the cytokine secretion profile. They are capable of determining a shift into anti-inflammatory cytokine pattern. Polyethylene glycol 2, transforming growth factor-b, and interleukin (IL)-10 are also up-regulated, with a contemporarily significant down-regulation of the pro-inflammatory cytokine pattern as interferon-c[31]. UC-MSCs can influence natural killer cell-mediated interferon- γ production. They suppress the causes of IL-12/IL-18 rise due to the phosphorylation of signal transducers and activators of transcription 4, nuclear factor-kB, T-bet activity and releasing of activin-A[32].

UC-MSCs also express nucleotide-binding oligomerization domain 2 capable of regulating the inflammatory intestinal background in adult animals, which is, as already known, linked with inflammatory bowel diseases such as Chron's disease. *In vivo* studies have shown how UC-MSCs administered in mice with colitis, thanks to the activation of nucleotide-binding oligomerization domain 2 with its ligand, muramyl dipeptide, increase anti-inflammatory responses, thus raising the production of IL-10 and other immune regulatory molecules such as forkhead box protein P3, transforming growth factor- β , arginase type Ⅱ , C-C motif chemokine ligand 22, heme oxygenase-1, and tumor necrosis factor α stimulated gene 6, promoting the infiltration of Treg cells and reducing the production of inflammatory cytokines. In particular, UC-MSCs injected into the bloodstream of mice do not reach the inflamed bowel directly but form aggregates in the peritoneum where they produce immunoregulatory molecules, including tumor necrosis factor-stimulated gene-6, that reduce intestinal inflammation[33,34]. Diabetes mellitus is a chronic metabolic disease consisting of uncontrolled high levels of glucose in the blood. Diabetes mellitus type 1 affects young people with autoimmune destruction of pancreatic β -cells[35] and is mainly in Th1 disease correlated with the synergic action of $CD4^+$ and $CD8^+$ cells on the β -cell destruction process. Moreover, Th17, with their interleukin and reduction in Treg concentration, may play a crucial role in triggering autoimmunity in the early stages of several autoimmune diseases, including diabetes mellitus type 1[36–39]. In a study by Montanucci *et al*, using an *in vitro* microencapsulated drug biohybrid UC-MSCs, they demonstrated the reduction of effector Th1 cells, the expansion of Treg cells which led to the rebalancing of the effector T cell/Treg ratio, up-regulation of indoleamine 2,3-dioxygenase 1, which is a master regulator of tolerance that mediates the differentiation in Treg. Nevertheless, no suppressive activity on Th17 cells was observed and the Th17 is insensitive to UC-MSCs immunomodulation[40]. Similar evidence was found in another autoimmune disorder, Sjögren's syndrome, using the same technology of the biohybrid drug system. Sjögren's syndrome is a systemic autoimmune disorder characterized by chronic inflammation of exocrine glands. In Sjögren's syndrome models, microencapsulated UC-MSCs reduce T cell proliferation. CPUC-MSCs in particular decrease both Th1 and Th17 cells in Sjögren's syndrome. They regulate several modified interferon-γ inducible factors that play a role in the immunomodulation effect such as indoleamine 2,3-dioxygenase 1, which is similar to an up-regulated diabetes mellitus model and inducible nitric oxide synthase[26]. *In vitro* studies demonstrated how MSCs and UC-MSCs cultured with specific growth-factors can differentiate into cells exhibiting features of hepatocytes. Interestingly, UC-MSCs express some hepatic markers as albumin, α -fetoprotein, connexin 3 and demonstrate that they are capable of being grafted as well as long-term self-maintenance in recipient livers[41]. Burra *et al* have standardized pre-*in vitro* isolation procedures to obtain a UC-MSCs population with hepatogenic properties that can be used for *in vivo* transplantation. Mice with UC-MSC transplants demonstrated a tendency to resolve liver damage rapidly, influencing inflammation in liver antioxidant enzyme activity and the inhibition of myofibroblasts and stellate cell activation[42].

Osteoarthritis is a degenerative chronic disease characterized by the degeneration and destruction of articular cartilage due to chondrocyte hypertrophy and apoptosis, together with changes in subchondral bone and osteophyte formation. Evidence shows that a soluble factor, named Kartogenin, is capable of differentiating MSCs into chondrocytes, thereby allowing new cartilage formation. Moreover, MSCs play a role not only in chondrogenic lineage differentiation

but also in modulating the immune response that leads to anti-inflammatory effects[28]. The UC-MSCs are another potential cell source for treating osteoarthritis characterized by a high expression of hyaluronic acid, sulfated glycosaminoglycans, and collagen. They exhibit CD276 that are observed in undifferentiated chondrocyte, indicating the immune privilege of UC-MSCs.

UC-MSCs are currently being studied in scaffolds smeared with human UC-MSCs with the aim of cartilage regeneration specific to three-dimensional polylactide-co-glycolide in rabbit models with a chondral defect, which has exhibited positive results[29]. Evidence has shown the ability of transplanted MSCs-derived neural stem cells to follow lineage under specific neuronal growth-factors, to survive and differentiate into progenitors or neuron-like cells expressing neuron-specific markers such as nestin, glial fibrillary acidic protein, β -tubulin Ⅲ, neuron-specific protein TH, and neuron-specific enolase[43]. Intracerebrally transplanted UC-MSCs can reach the ischemic brain injury in rat models. After implantation, UC-MSCs are detectable in the damaged area expressing neuron-specific markers[44,45]. Moreover, a reduction in the number of activated microglia, blocking immune cell infiltration activity, as well as a remarkable reduction of the extensive neuronal damage were observed, occurring during the ischemia-reperfusion and demonstrating the cytoprotective activity of UC-MSCs[46]. This cytoprotective activity is mostly correlated with the immune-regulatory effect of UC-MSCs transplanted due to the modulation and scavenging of the host body's immune response cells under inflammatory conditions as a result of a stroke. They can also enhance the proliferation of endogenous neurogenesis by suppressing apoptosis, secreting neurotrophic factors and inducing vascularization and angiogenesis[47]. A similar effect on traumatic brain injury in rat models was investigated, where UC-MSCs transplantation combined with hyperbaric oxygen treatment resulted in the significant recovery of neurological and cognitive functions[48]. This was also noted in rat models with spinal cord injury where intravenous or intraspinal transplantation of UC-MSCs showed a neuroprotective effect[49]. There are interesting studies concerning the effect of UC-MSCs in some neurodegenerative diseases such as Parkinson's disease. Parkinson's disease is characterized by a continuous dopaminergic cell loss in the nigrostriatal dopaminergic system at the basal ganglia. Authors demonstrated that the transplantation of neuronal differentiation into a dopaminergic phenotype of UC-MSCs in a Parkinson's disease rat model can reduce the symptoms of the disease[50]. Liu *et al*, investigating the protective effect of UC-MSCs related with a multifunctional mediator, hepatocyte growth factor on the Parkinson's disease cell model, showed the ability of UC-MSCs + hepatocyte growth factor in promoting the regeneration of cells damaged by Parkinson's disease through the regulation of intracellular Ca^{2+} levels[51].

Endometriosis is a common, benign, estrogen-dependent and chronic gynecological disorder characterized by the presence of endometrial glands and stroma outside the uterine cavity that cause chronic pelvic pain and infertility[52-61]. Several non-resolutive strategies, both surgical and medical, are used against this disease[62-64], but today stem cell therapy is a promising new and unprecedented strategy[65]. Among the several sources of stem cells, UC-MSCs are the strongest candidates for cell-based therapy. The presence of nerve fibers in endometriosis lesions are well known in literature and they play a role in both pathogenic and symptomatic manifestation[66,67].

UC-MSCs have a specific use in therapies that include the use of cells. Moreover, they demonstrate anticancer effects on solid tumors mediated by cell-to-cell and/or non-cellular contact mechanisms. When UC-MSCs were used in mice with mammary adenocarcinomas, they demonstrated the ability to migrate to metastatic tumor sites, suggesting their homing abilities. This anticancer effect with a reduction of growth rate was observed also in ovarian cancer, osteosarcoma and breast adenocarcinoma[68-78]. Several molecules are produced by UC-MSCs, including cytokines, glycosaminoglycans, hyaluronic acid, chondroitin sulfate, cell adhesion molecules, and growth factors, which play a role in the anticancer effect[79-88].

3.6. Human protocols

Several *in vitro* and *in vivo* studies have shown already that UC-MSCs are safe and non-tumorigenic both in laboratory animals and non-human primates[83], and some clinical trials have already started. For example, MSCs, UC-MSCs included, can be administered to patients with autoimmune and chronic diseases such as Crohn's disease. Some phase 3 clinical trials are currently ongoing with the aim to confirm the safety and the efficacy of this new therapy. Multiple administration of both autologous and allogeneic MSCs, derived from various sources including bone marrow, adipose tissue, and UC treatment, are feasible and have not been associated with any serious adverse event; principally, no tumor formation has been documented in humans until now. Furthermore, studies are underway in order to confirm the efficacy in fistulizing Crohn's disease[89], and although stem cell therapy is not already a standard treatment for inflammatory bowel diseases, it may become a useful treatment, especially for severe or recurrent inflammatory bowel disease patients[90]. Multiple sclerosis is an immunologically mediated disease of the central nervous system. Several clinical trials were done to investigate the safety and the possible use of MSCs in multiple sclerosis, UC-MSCs included[91]. Hou *et al* underlined the effectiveness and the safety of UC-MSCs, and they also demonstrated that the inflammatory activity was significantly reduced after treatment. Furthermore, no other clinical relapse and no new magnetic resonance imaging lesions were detected in a 4-year treatment period. This evidence highlights the need to proceed with clinical trials in order to explore MSCs transplantation as a potential new therapy for patients with aggressive multiple sclerosis[92].

Hypertensive diseases during pregnancy affect almost 10% of women worldwide and are categorized into gestational hypertension, chronic hypertension, and preeclampsia/eclampsia[93-101]. UC-MSCs in patients with preeclampsia show high expression of neuroglial markers, suggesting a commitment to neuroglial differentiation, thus transplantation of exogenous uncommitted MSCs may be a viable option for the treatment of preeclampsia[102-104].

3.7. Cell–free therapy and MSCs as drug vehicles

Although our systematic review focused on UC-MSCs, we must consider another two aspects in the clinical and therapeutic application of stem cells. The first is the cell-free therapy through microvesicles and exosomes derived from stem cells. Exosomes, small lipid vesicles of 40-130 nm, and microvesicles, larger than exosomes (100-1 000 nm), are included in the larger group of extracellular vesicles and they are secreted from MSCs[105]. Some studies, in fact, affirm that the MSCs play a regenerative role through a paracrine mechanism microvesicle-mediated[106,107]. Extracellular vesicles have the ability to carry nucleic acids, proteins and lipids with several roles: in biochemical processes by donating miRNAs that can silence the RNA translation, in inflammation by carrying and transferring inflammatory cytokines, in cell-to-cell communication[105,107]. Furthermore, the RNAs carried by extracellular vesicles maintain their function showing the role of extracellular vesicles in epigenetic signalling[105]. For these reasons, microvesicles and exosomes have shown to influence injuries, infections and diseases with a high number of clinical and therapeutic applications: they have shown a cardio, renal and neuroprotective activity, a role in pancreas recovery, pneumonia, pulmonary hypertension, acute respiratory disease syndrome, the prevention of silico-induced lung fibrosis, against liver fibrosis[107,108]. Furthermore, they help re-epithelization by inducing cellular proliferation and angiogenesis[108] and they have shown an immunomodulatory role in systemic lupus erythematosus[107]. However, further studies are needed to evaluate the possible therapeutic application of extracellular vesicles in clinical practice. The second aspect is the drug delivery using MSCs as vehicles. MSCs, in fact, have some important advantages in target therapy due to their homing and self-maintenance capability and inflammatory microenvironment interaction[109]. MSCs have been engineered to express anti-proliferative, pro-apoptotic and anti-angiogenic factors for the treatment of several diseases. The most common application is for the treatment of cancer: MSCs, in fact, can localize and integrate into tumor stroma and deliver anti-cancer agents or oncolytic viruses[110]. In the end, MSCs can play in different ways a crucial role in future therapies.

4. Discussion

Among MSCs sources, UC-MSCs as a resource seem to possess some brilliant advantages. UC-MSCs can be collected by a simple procedure after delivery, reusing a waste product and applying it for autologous or allogeneic procedures. Furthermore, these cells show multipotency, low immunogenicity, and immunosuppressive activity. These properties give hope for several different clinical applications[79]. Several pre-clinical *in vitro* and *in vivo* studies have shown the safety and the ability of these special cells in homing, adhesion, proliferation and differentiation into specific lineages and functions; the capacity to reply to surrounding signals, conditioning the behaviour of neighbour cells, as well as the capacity to regulate cellular and tissue processes such as tumorigenesis, inflammation, apoptosis and proliferation. These qualities are opening up new therapeutical scenarios, as some clinical trials are currently demonstrating for different degenerative, chronic and inflammatory diseases.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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