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Placenta-Derived Mesenchymal Stem Cells for Treatment of Diseases: A Clinically Relevant Source

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The placenta is an organ that is discarded after childbirth. Recently, mesenchymal stem cells (MSCs) isolated from various parts of the placenta (PMSCs) are established as a rich, allogeneic, and sustainable source of MSCs in comparison to bone marrow MSCs (BM-MSCs). PMSCs can be banked postnatally for future autologous and allogeneic applications in the treatment of diseases. PMSCs can be categorized as an intermediary between BM-MSCs and embryonic stem cells (ESCs) as it is devoid of adverse aspects associated with the employment of ESCs accompanied with primitive and enhanced properties in comparison to BM-MSCs. PMSCs are employed in the treatment of various diseases including cancer, neurological, bone, and cardiovascular disorders. This utility of PMSCs is due to its superior inherent characteristics in comparison to BM-MSCs, which renders PMSCs more attractive for clinical translation. Herein, this review describes the superior inherent characteristics of PMSCS in contrast to BM-MSCs including accessibility, higher expansion abilities, enhanced immunomodulatory and immunosuppressive properties, ability to differentiate beyond mesodermal lineages, pathotropic and regenerative abilities, lower immunogenicity, and anti-cancer strategy that are correlated to its therapeutic application in the treatment of various diseases including corona virus infection started in 2019 in recent preclinical and preclinical studies.

1. Introduction

Mesenchymal stem cells (MSCs) have generated a lot of hype for the treatment of a plethora of diseases, with almost 1092 registered clinical trials and 330 completed trials involving MSCs listed in the clinical trials database (http://clinicaltrials.gov). Out of these 330 completed trials, 29 studies were published with promising clinical outcomes in various diseases such as diabetes, Alzheimer's, cardiovascular condition, etc. Consequently, MSCs are employed as treatment or delivery systems and has demonstrated enhanced outcomes.[1] MSCs are exploited due to its validated efficacy in differentiation,[2] immunomodulation and immunosuppression,[3] intrinsic migratory affinity toward injured tissue or tumor microenvironments,[4] and anti-cancer consequences in various tumor types.[5]

Generally, stem cells (SCs) can be categorized into two wide groups, embryonic (ESCs) and adult SCs (**Figure 1**).ESCs are derived from the inner cell mass of the blastocyst of a human embryo that is developed post in vitro fertilization of the egg.[6] These cells are pluripotent, with the ability to proliferate indefinitely and differentiate into all three germ layers.[7] Nonetheless, ESCs can develop teratomas after inoculation as a result of unregulated differentiation due to the presence of oncogenes and trisomies.[8] Hence, employment of ESCs as a therapeutic tool is often accompanied with major safety concern.[8] Additionally, ESCs are procured via the destruction of the blastocyst of a human embryo, hence elicits ethical issues and controversy which impedes its clinical translation.[9]

Adult derived SCs are an alternative source of SCs that can provide clinical application whilst excluding ethical and teratoma formation associated with ESCs.[10] A specific subset of adult SCs, identified as MSCs, have produced intense hype as a strategy for treating multiple disease conditions. Previously, MSCs were first discovered by Friedenstein in the stromal compartment of bone marrow.[11] Subsequently, MSCs were successfully isolated and characterized from various niches such as skin, dental pulp, adipose, extraembryonic (i.e., umbilical cord [UC] and placenta), and fetal tissues.[2a,12] Nonetheless, bone marrow derived MSCs (BM-MSCS) are the most characterized and broadly investigated source of MSCs.[13]

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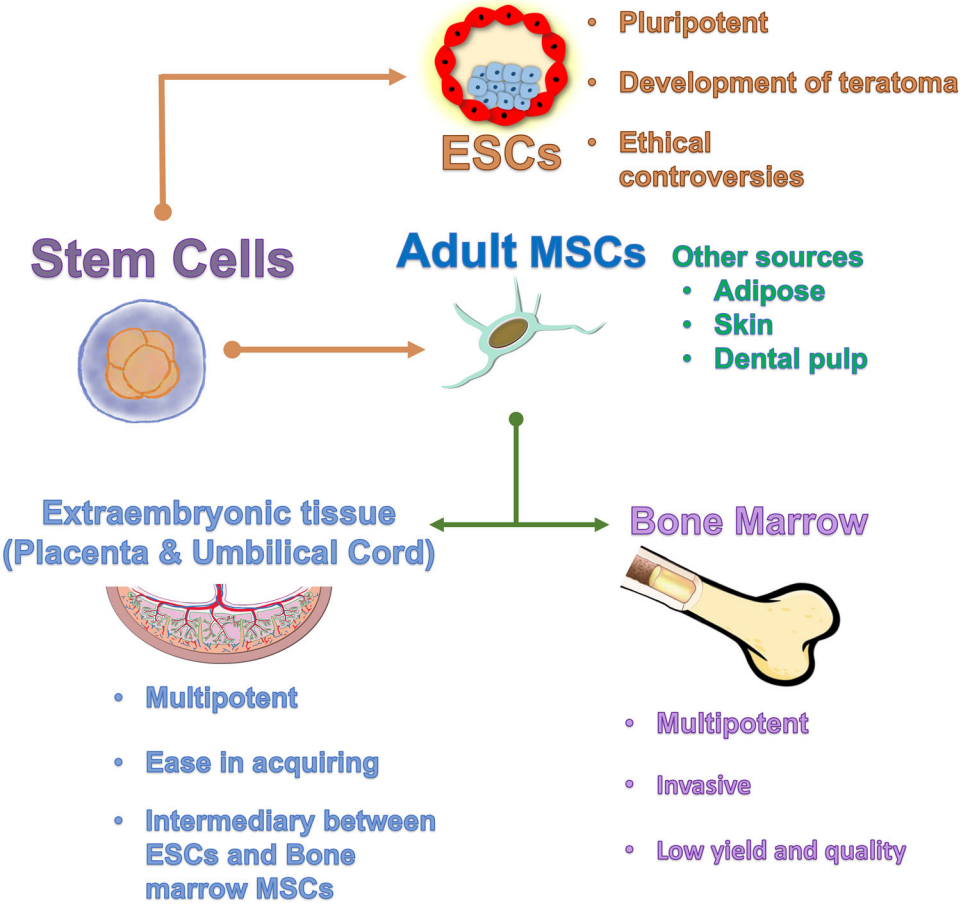

Figure 1. Broad classification of stem cells into embryonic and adult mesenchymal stem cells. Adult MSCs can be isolated from various sources including extraembryonic tissue (placenta and umbilical cord) and bone marrow.

Interestingly, MSCs have no exclusive phenotypic marker.[14] However, the International Society of Cellular Therapy (ISCT) have presented standardize criteria for the characterization of a "true" MSCs.[14,15] Specifically, MSCs 1) are plastic-adherent in culture; 2) express CD73, CD90, and CD105 markers as quantified by flow cytometry in ≥95% of population; 3) lack expression of haematopoietic markers CD11b, CD14, CD19 or CD34, CD45, or CD79a and major histocompatibility complex(MHC) II molecules (≤2% positive expression); and 4) differentiate into adipocytes, chondroblasts, and osteoblasts, under standard in vitro differentiating conditions.

Our review highlights the distinct characteristics of MSCs isolated from various perinatal tissues including advantages and drawbacks correlated to its therapeutic application and clinical translation. Notably, this is the first review that discusses how MSCs from specific parts of the placenta displayed promising therapeutic potential and were exploited in the treatment of various disorders including degenerative diseases, cancer, and the recent corona virus infection (COVID-19) that started in 2019. In addition, our review provides an updated discussion on the most recent preclinical and clinical applications of PMSCs in the past 6 years and challenges involved in its clinical translation. The most recent review on a similar topic was published in 2021 by Chia et al., which discussed preclinical and clinical studies using MSCs derived from the placenta and UC solely for the treatment of bronchopulmonary dysplasia.[16] Additionally, there are three other reviews that discussed MSCs in general, with no clear delineation of MSCs origins when in fact there are inherent differences between MSCs isolated from various sources, which are highly relevant to its therapeutic utilization and clinical translation.[14,17] Another similar review, a book chapter by Torre et al., discussed the therapeutic applications of placenta derived MSCs in the treatment of various diseases in both preclinical and clinical settings, categorizing the review based on the disease types. However, this review was published almost 4 years ago. Therefore, our review delivers an updated discussion on the therapeutic ability of MSCs from various parts of the placenta and its recent preclinical and clinical developments in various diseases including COVID-19 and challenges implicated in its clinical translation.

2. Placenta: A Rich and Sustainable Source of MSCs for Clinical Applications

2.1. Drawbacks of Other Adult Stem Cell Sources

MSCs isolated from the bone marrow and adipose tissue are commonly employed as treatment strategies in various preclinical

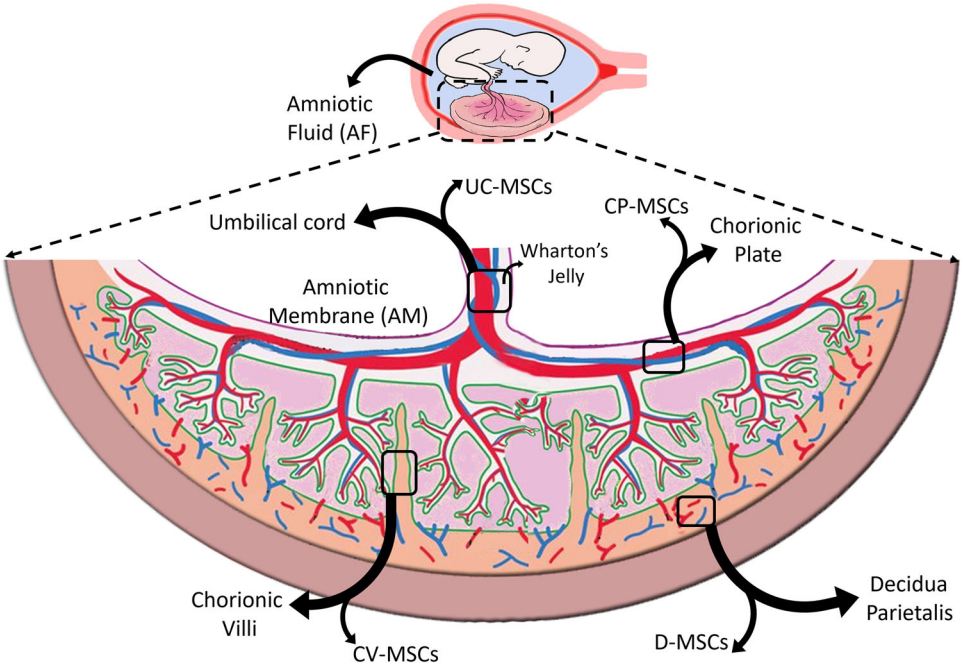

Figure 2. Schematic representation of various sources of MSCs in a human term placenta. UC-MSCs: umbilical cord-mesenchymal stem cells; CP-MSCs: chorionic plate-mesenchymal stem cells; CV-MSCs: chorionic villi-mesenchymal stem cells; D-MSCs: decidua parietalis-mesenchymal stem cells.

and clinical reports, with 190 and 145 clinical trial studies respectively till date.[18] Nonetheless, several drawbacks are involved in the utilization of BM-MSCs, which can hinder its long-term clinical translation. Procedure involved in procuring BM-MSCs are highly invasive and uncomfortable.[7b] Importantly, not only does the yield and quality of isolated SCs decline with age but employment of patient's own MSCs is not feasible as cell quality may be impacted by specific disease or genetic conditions.[19] Hence, an alternative source of allogeneic MSCs is essential for efficacious and sustainable clinical applications, such as the placenta.[20]

2.2. Advantages of MSCs Sourced from the Placenta

A human placenta is the first structure to develop during embryogenesis and an embryo will not survive without a placenta. Consequently, a human placenta essays an integral function in fetal development, nutrition, and maintenance of tolerance in the mother's body.[21] Recently, the placenta has gained additional interest because it contains a pool of various types of SCs, including MSCs.[22] Typically, placenta is disposed post-partum and hence not difficult to acquire. A human placenta comprises tissues of both fetal and maternal origin.[23] Placenta can be categorized into the maternal (decidua parietalis [DP]) and fetal (amniotic membrane [AM], amniotic fluid, chorionic plate [CP], chorionic villi [CV] , and UC/Wharton's Jelly) origin (**Figure 2**). Subsequently, placenta MSCs or PMSCs will be used as a general term to represent MSCs isolated from the placenta, not taking into consideration the specific region from which they were isolated.

MSCs isolated from extra-embryonic tissues (placenta and [UC]) exhibits similar fundamental characteristics with BM-MSCs such as expression of specific markers, ability to differentiate, and adherence to plastic as stipulated by ISCT.[18a]

In comparison to BM-MSCs and ESCs, MSCs from the placenta can be isolated non-invasively and does not raise ethical concerns. Interestingly, unlike other adult MSCs, MSCs from extra-embryonic tissues such as the placenta express ESC specific markers including Nanog homeobox protein, octamer- binding transcription factor, Tra-1-60, Tra-1-81, stage specific embryonic antigen-3, and stage specific embryonic antigen-4 which are critical pluripotent markers that maintains cell's "stemness" or ability to remain an undifferentiated state.[8] Hence, in comparison to BM-MSCs, PMSCs possess more advantageous properties including greater proliferation capacity (doubling times), with broader differentiation abilities.[24] This is likely due to the fact that the placenta essays a vital function in the growth of the developing fetus.[25] PMSCs also displayed faster growth kinetics, higher engraftment properties and greater colony-forming unit fibroblast developing ability.[24a] Additionally, PMSCs exhibit superior immunomodulatory and immunosuppressive properties.[26] PMSCs lack or express lower levels of human leukocyte antigen class I, and hence have lower immunogenicity than adult BM-MSCs.[26]

Hence, MSCs isolated from placenta have established itself as an intermediary between BM-MSCs and ESCs.[26] Therefore, PMSCs demonstrates specific characteristics that may avert undesirable effects correlated with the clinical utilization of ESCs, such as a lack of tumorigenicity and reduced ethical concerns.[27] From the clinical perspective, as PMSCs are younger cells, they are exposed to reactive oxygen species (ROS)and other physical and chemical stressors in a shorter period.

PMSCs can also be banked postnatally for future autologous and allogeneic applications in the treatment of diseases. Fur-

Table 1. Summary of the use of placenta mesenchymal stem cells of diverse origins in animal disease models within the last 7 years.

MSCs	Origin	Animal model	Disease treated	Outcome	Ref
PMSCs	Human	Mice	Colon cancer model	Cells engineered with herpes simplex virus effectively inhibited colon cancer progression and metastasis	[31]
PMSCs	Human	Rat	CCl_4-injured rat liver model	Cells repaired liver fibrosis and significantly reduced TGF-β1 and α-SMA expression generated by CCl_4 in rats.	[30a]
PMSCs	Human	Mice	Chronic heart failure	Intramuscular injection of cells improved left ventricular systolic and diastolic function and reduced interstitial fibrosis in comparison to control group.	[32]
CV- MSCs	Human	Rat	Myocardial infarction	Cardiac improvement was indicated by a reduction in left ventricular end-diastolic diameter, reduction in left ventricular end-systolic diameter, and increased left ventricular ejection fraction and left ventricular shortening fraction.	
Amnion-derived MSCs blood vessel-derived MSCs from the chorionic plate and Wharton's jelly-derived MSCs from the UC	Human	Mice	Skin wounds	All three PMSC types demonstrated similar advantageous effects on wound healing and neovascularization in mouse model.	[33]
PMSCs	Human	Mice	Mouse hindlimb ischemia	Cells significantly enhanced micro vessel density, enhanced blood perfusion, and reduced pathologies in ischemic mouse hindlimbs as compared to those in the control group.	[30c]
PMSCs	Human	Rats	Critical limb ischemia in diabetes model	Cells quickened recovery of ischemia via newly formed capillaries, increased arterioles, and secretion of various pro-angiogenic factors.	[30d]
DP-MSCs	Human	Mice	Experimental autoimmune encephalomyelitis (EAE)	Treatment of animals already presenting with moderate symptoms resulted in mild EAE with reduced disease scores. Treatment inhibited T-cell proliferation via downregulation of IL-17 production	[34]
PMSCs	Human	Mice	Duchenne muscular dystrophy	PMSCs resulted in decreased creatine kinase levels. PMSCs significantly decreased the expression of TGF-β and the level of fibrosis in the diaphragm and cardiac muscles, inhibited inflammation, and increased utrophin expression.	[35]

thermore, their superior attributes in comparison to BM-MSCs, which includes higher expansion capabilities, phenotypic plasticity, enhanced immunomodulation, lower immunogenicity, and availability makes PMSCs more apt for clinical translation.

Recently, a study investigated the secretion of various growth factors and cytokines (human growth factor [HGF], vascular cell adhesion protein 1, transforming growth factor beta 1 [TGF-β1], vascular endothelial growth factor [VEGF] , insulin-like growth factor-1, and prostaglandin E_2), that have been established to play an integral role in inhibition of fibrosis, angiogenesis, and apoptosis in four populations (DP, AM, CP, and UC) of PMSCs.[22] Furthermore, they established that different populations of PMSCs displayed substantial variations in the levels of specific cytokine secretions. The different paracrine secretion profile between PMSCs from different sources of perinatal tissues suggests its diverse biological potential in treatment of diseases. Correspondingly, Zhu et al. demonstrated that fetal PMSCs expressed significantly higher levels of HGF than maternal PMSCs.[20] HGF is a growth factor that promotes tissue repair, angiogenesis and is involved in regulatory function by inducing dendritic and regulatory T-cells.[28] This suggests that PMSCs from fetal origin may have a superior advantage in terms of therapeutic applications in comparison to PMSCs from maternal origin.[20] Nonetheless, further investigation must be carried out to understand the biological characteristics to identify advantages and limitations of PMSCs from particular perinatal tissues to match its potential to the treatment of specific diseases. These data may provide clear indications to appropriate clinical applications of different types of PMSCs from perinatal tissues.

3. Placenta Derived MSCs: A Promising Therapeutic Potential

PMSCs were first defined in 2004, garnering intense hype as a superior alternative of MSCs for therapeutic application in many disease conditions.[29] Hence, this led to many research studies investigating the therapeutic potential of PMSCs in various preclinical models including myocardial infarction (MI), ischemia, liver fibrosis, etc. (**Table 1**).[30]

Moreover, there are almost 40 completed clinical trials listed in the clinical trials database (http://clinicaltrials.gov), encompassing the employment of MSCs from various sources of the placenta in the treatment of diverse diseases. The latest completed clinical trials outcome is tabulated in this review (**Table 2**). The research of these studies demonstrated promising and optimistic outcomes.[26]

PMSC therapies have attracted interest as a highly promising strategy to combat many diseases.[47] The utility of PMSCs is a result of its key characteristics, which include (**Figure 3**) 1) differentiation capabilities,[48] 2) immunomodulatory and immuno-

Table 2. Completed clinical trial studies employing the use of MSCs derived from various parts of the placenta for the treatment of diseases.

Identifier	Source of MSC	Disease	Phase	Treatment summary	Outcome
NCT02481440	UC- MSCs	Spinal cord injury	1/2	Four intrathecal transplantations of hUC-MSCs (1×10^6 cells kg^{-1}) monthly and were seen in follow-up four times (1, 3, 6, and 12 months after final administration) was performed.	Safety and efficacy evaluations were performed in 102 and 41 subjects, respectively. Demonstrated substantial improvement in neurological dysfunction and recovery of quality of life based on the mean total scores as outlined by the SCI Functional Rating Scale of the International Association of Neurorestoratology (IANR-SCIFRS) and American Spinal Injury Association (ASIA) at the final follow-up in comparison with baseline data.[36]
NCT04520022	UC- MSCs	Recessive dystrophic epidermolysis bullosa	1/2a	3 intravenous injections of hUC-MSCs (1×10^6 to 3×10^6 cells kg^{-1}) every 2 weeks and followed up for 8–24 months after treatment.	Treatments were well tolerated with no serious adverse effects in four adults and two paediatric subjects. All six patients demonstrated reduced blister count, disease, and pain severity score in the affected areas.[37]
NCT02172937	- DP-MSCs	Severe acute graft-versus-host disease (GVHD)	1/2	Grade II–IV patients were infused intravenously with (0.9 to 2.9 × 10^6 cells kg^{-1}), with a median of 2 doses 1 week apart.	All 21 patients treated responded by day 28. Complete resolution of GVHD was seen in 11 patients. 1-year survival in treated patients was 81%. 4-year survival in treated patients was 57%.[38]
NCT04224207	UC Wharton's jelly derived MSCs	Retinitis pigmentosa	3	Subtenon orbital injections of $2–6 \times 10^6$ cells in patients followed by 12-months evaluation.	Statistically significant increase in visual field and ellipsoid zone width parameters were detected in 19/34 eyes (55.9%). The disease remained stable in 13/34 eyes (38.3%) in the first year.[39]
NCT02644447	UC- MSCs	Premature ovarian failure (POF)	1/2	10×10^6 MSCs were injected into the ovary of patients under transvaginal ultrasonographic (TVUS)-guidance. MSCs were implanted with (8 subjects) or without collagen (6 subjects) scaffolds to the ovaries of POF patients.	MSCs treatment restored overall ovarian function as demonstrated by increased estradiol concentrations, improved follicular development, and increased in antral follicles in 6/14 subjects. Importantly, 2/14 subjects conceived naturally in women with POF after treatment.[40]
NCT02172963	DP- MSCs	Hemorrhagic cystitis (HC)	1/2	Patients with HC of grades 3–4 were treated with intravenous infusion of 1 dose of cells (1.5×10^6 cells kg^{-1}).	In half the patient's cohort (total: 11 subjects), HC disappeared within 5 days after cell infusion. Patients treated with MSCs within 3 days after the start of HC had a duration of HC of 5 days and a shorter duration of pain than patients who were given treatment later.[41]

(*Continued*)

Table 2. (Continued).

Identifier	Source of MSC	Disease	Phase	Treatment summary	Outcome
NCT02034188	UC-MSCs	Multiple sclerosis	1/2	Patients were treated with seven intravenous infusions of 20×10^6 cells over 7 days. Efficacy was assessed at baseline, 1 month, and 1-year post treatment.	MRI scans of the brain and the cervical spinal cord showed inactive lesions in 15/18 (83.3%) subjects after 1 year. Overall, treatments in 18 subjects are safe with no serious adverse effects and improved quality of life is reported.[42]
NCT01413035	UC- MSCs	Type 2 Diabetes Mellitus (T2DM)	1/2	MSCs (1.0×10^6 cells kg^{-1}) were transfused intravenously in 3 times	MSC transfusion is safe and well tolerated in 18 subjects, successfully reduced blood glucose, and increases the generation of C-peptide levels and regulatory T cells in a subgroup of T2DM patients.[43]
NCT02395029	Placental matrix-derived mesenchymal stem cells	Peyronie's disease (PD)	1	1.0 cc of MSCs (number of cells not mentioned in the paper) were injected intracavernosally and followed up at 6-week, 3-month, and 6-month intervals to document changes in plaque volume, penile curvature, and erectile function status	Of a total of ten plaques managed, seven had disappeared completely at 3-month follow-up in all five subjects. MSCs may be beneficial and effective as a nonsurgical treatment in patients with PD.[44]
NCT02398370	Placental matrix-derived mesenchymal stem cells	Mild to moderate erectile dysfunction (ED)	1	1.0 cc of MSCs (number of cells not mentioned in the paper) were injected intracavernosally and was followed up with at 6 weeks, 3 months, and 6 months to assess peak systolic velocity (PSV), end diastolic velocity, stretched penile length, penile width, and erectile function status based on the International Index of Erectile Function questionnaire.	At the 6-week follow-up, 2/8 patients for whom previous oral therapies failed had the ability to sustain erections on their own. At the 3-month follow-up, 1 additional patient was able to achieve erections on his own.[45]
NCT02313415	UC- MSCs	Uterine infertility	1	1×10^7 MSCs loaded into collagen scaffold were implanted into the uterine cavity following an adhesion separation procedure. Endometrial proliferation and differentiation were assessed after therapy.	Improvement in endometrial proliferation, differentiation, and neovascularization following treatment. After 3 years, 10 out of 26 patients had become pregnant, and eight of them had delivered live babies with no obvious birth defects and without placental complications.[46]

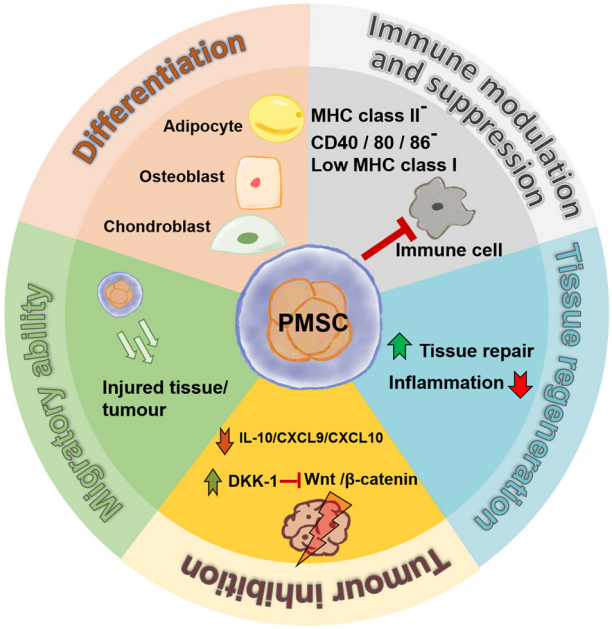

Figure 3. Schematic representation of key characteristics of PMSCs that contribute to its therapeutic employment in the treatment of diseases.

suppressive properties,[3] 3) inherent tropism to injured tissue or tumor microenvironments,[4] and 4) inhibitory effects on several tumors.[5] The therapeutic application of PMSCs via these vital attributes will be discussed further in this review.

There are also inherent differences between fetal PMSCs and maternal PMSCs.[22] Whilst there are several investigations comparing phenotypical and functional characteristics of PMSCs isolated from various parts of perinatal tissues, the origin of MSCs (AM, CP, DP, or UC) where they were procured from have not been clearly defined.[49] Furthermore, a thorough evaluation comparing MSCs from various parts of the perinatal tissues and ideal sources for particular clinical applications has not been clearly elucidated.

3.1. Immunomodulatory and Immunosuppressive Properties

Generally, MSCs ability to modulate the immune system is well-documented, via a synergy of cell dependent and soluble factors.[50] MSC-mediated immune modulation occurs mainly through the regulation of T-reg cells which has been demonstrated to inhibit the migration of peripheral blood mononuclear cells and impede cytotoxic function of natural killer (NK) cells and T cells.[50] When MSCs are administered in the body, it triggers an immune reaction which stimulates MSCs to release cytokines, growth factors, and chemokines which regulates immune cells and repairs injured cells by inhibiting immunological response. Moreover, allogeneic MSC transplants survive longer than other allogeneic cells.[51] As MSCs express low levels of MHC Class I molecules, they are more receptive to targeted killing by NK cells.[51,52] Hence, MSCs immune tolerance allows clinical utilization of allogeneic MSCs from the placenta. Adult MSCs from most tissue sources lack expression of MHC class II molecules and co-stimulatory molecules such as CD40, CD80, or CD86, which allows elusion of recognition by immune cells leading to escape from immune surveillance.[53] A recent clinical study in the treatment of Graft-versus-host disease established that maternal DP-MSCs are more immunosuppressive than other sources of stromal cells, including those from commonly utilized bone marrow.[54] Results from their pilot study demonstrated that patients treated with DP-MSCs showed partial or complete efficacy and the best 1-year survival. Importantly, DP-MSC treatment was well tolerated in all patients with no adverse reactions. This is not surprising as the placenta itself can be acknowledged as an immune organ as it allows maternal-fetal immune privilege to ensure the sustenance of the allogeneic fetus. Additionally, in comparison to BM-MSCs, PMSCs demonstrated enhanced shift in monocyte differentiation from inflammatory M1 macrophages to non-inflammatory M2-like macrophages.[55] Hence, this data suggest that PMSCs may exert an improved reduction in inflammation associated disease condition

Wu et al. compared four populations of MSCs derived from different perinatal tissues including DP, AM, CP, and UC.[22] This study established that MSCs from the fetal origin has a notably greater proliferative capacity than MSCs from maternal origin. CP-MSCs displayed highest expression of CD 106, which is a marker involved in immunomodulation and immunosuppression of MSCs. CD 106 is involved in embryonic development specifically in the formation of UC and placenta. Hence, this vital characteristic of CP-MSCs provides promising potential for clinical translation. F-PMSCs have also been validated to show stronger immune modulatory function.[20] As recently reported, MSCs from fetal origin express higher levels of CD 200, which is a cell surface glycoprotein that facilitates immunosuppressive signal through the modulation of macrophage and dendritic cell responses.[56] CD 200 can regulate the cytotoxic effects of NK cells and potentially responsible for the increased ability of fetal derived MSCs to block NK cells in comparison to maternal derived MSCs.

3.2. Differentiation beyond Mesodermal Lineages

Similar to its other adult counterparts, PMSCs have tri-lineage differentiation abilities to form adipocytes, chondrocytes, and osteoblasts. Recently, Rahimi-Sherbaf et al. has demonstrated the ability of PMSC to differentiate into various neural cell lineages on nanofibrous scaffold suggesting that PMSCs have a subpopulation of cells that are able to differentiate into neurogenic cells.[57]

PMSCs have also been shown to differentiate into cardiomyocytes and survive for at least 2 months in the scar tissue after implantation into the hearts of a MI rat model.[58] Another study in MI rat model displayed a prolonged cardiac function 8 months after i.v. injection of PMSCs.[59] Tissue specific differentiation of PMSCs may play a minor role in the multifaceted mechanisms underlying the therapeutic effects of these cells.[48]

A recent study has established that there is quantitative variation in differentiation abilities between different population (DP, AM, CP, and UC) of MSCs from perinatal tissues. Results from this study demonstrated that AM-MSCs displayed lower differentiation potential in comparison to three other populations of MSCs.[22] In particular, AM-MSCs could only differentiate to os-

teocytes and adipocytes and not chondrocytes. Interestingly, this study established that MSCs from the fetal origin has a notably greater proliferative capacity than MSCs from maternal origin.[22] Hence, the proliferative potential of PMSCs did not correlate to its differentiation potential. In contrast, an older study concluded that MSCs from fetal origin displayed higher osteogenic differential potential in comparison to MSCs from maternal origin, the origin of MSCs (AM, CP, DP, or UC) have not been clearly defined in this paper and fetal MSCs were simply termed as F-MSCs.[20]

As mentioned previously, this highlights a critical issue in the field of MSC based therapies from perinatal tissues. Whilst many studies are conducted to investigate phenotypical and functional characteristics of MSCs isolated from various parts of perinatal tissues, the origin of these MSCs (AM, CP, DP, or UC) are not clearly distinguished.

3.3. Pathotropic and Regenerative Ability

MSCs have a distinctive and inherent ability to migrate and home to sites of injured tissues, including inflammation and tumor microenvironment.[60] MSC based therapies have been utilized in various disease models associated with tissue damage, inflammation and have led to successful tissue repair and regeneration.[2b,60] PMSCs injected into mice with hindlimb ischemia migrated and reduced inflammation accompanied with promoted regeneration of blood flow in the injured tissue.[61] Reiter et al. have demonstrated that intra-tracheal injection of MSCs have improved lung alveolarization, angiogenesis, and inflammation in rodent model with hyperoxia-induced lung injury through secretion of SDF-1.[62]

Spinal cord injury is a debilitating disease which involves permanent disability that includes several symptoms that reduces the quality of life of patients. Unfortunately, till date, there has been a lack of any effective treatment. Recently, clinical trial data demonstrated that intrathecal injection of UC-MSCs in 102 patients with chronic spinal cord injury showed effective and promising outcome.[36] Patients were injected with 1×10^6 cells kg^{-1} once a month for a period of 4 months consecutively and treatment displayed substantial improvement in neurological function and recuperation of their quality of life.[36] Notably, treatments were safe, and no serious adverse effects were documented.

Duchenne muscular dystrophy is a degenerative disease of the cardiac and skeletal muscles that is triggered by aberrations in the dystropin gene. Recently, Bier et al. demonstrated that PMSCs and its secreted exosomes increased in vitro differentiation of human muscle cells derived from Duchenne muscular dystrophy patients.[35] Notably, in vivo data from their group demonstrated that PMSCs and its secreted exosomes triggered a synergistic therapeutic effect by decreasing inflammation and fibrosis and increasing utrophin expression in X-linked muscular dystrophy mice model.[35] The therapeutic effects of PMSCs were ascribed to paracrine signaling via MSCs secretions and through physical communication between MSCs and diseased microenvironment. MSCs secrete many cytokines, chemokines, and growth factor, which play a critical role in local cellular functions.[63] These molecules have established anti-apoptotic and regenerative capabilities.[64]

Inflammatory bowel diseases such as ulcerative colitis and Crohn's disease progresses to a common and severe complication such as intestinal fibrosis. Recently, Choi and co-workers investigated the effect of PMSCs and UC-MSCs on ameliorating fibrosis in human primary intestinal myofibroblasts (HIMFs).[65] They established that UC/PMSCs suppresses TGF-β1-induced fibrogenic activation in HIMFs via blocking the Rho/MRTF/SRF signaling pathway.[65]

Previous clinical study with UC-MSCs treatment displayed improved liver function and ascites in decompensated liver cirrhosis patients.[66] Moreover, preclinical studies have demonstrated successful reduction in fibrosis in various organs via inhibition of TGF-β activation via ROS reduction. These previous studies have employed the use of BM-MSCs and adipose derived MSCs. Nonetheless, the use of BM-MSCs encompasses several drawbacks that have been discussed above in this review.

Recently, priming of MSCs has been adopted to enhance therapeutic efficacy and application of cell treatment.[67] This include conditioning MSCs with pharmacological drugs, hypoxic condition, cytokines, or specific cell culture conditions.[67] In comparison to naïve MSCs, Zhilai and colleagues demonstrated the ability of UC-MSCs that were primed in hypoxic condition to induce higher levels of HGF, VEGF, and brain-derived neurotrophic factor which are critical in neural regeneration.[68] Importantly, these implanted preconditioned UC-MSCs displayed enhanced migratory potential, engraftment, and improved tissue function in a rat spinal cord injury model.[68] Additionally, another study by Mathew et al. revealed that PMSC preconditioned in hypoxic settings regulate themselves by increased expression of glucose transporters, stimulation of insulin and displayed enhanced angiogenic potential thus rendering them more apt for wound healing and regeneration.[69]

3.4. Anti-Cancer Strategy

There is accumulative evidence suggesting that PMSCs can be exploited as therapeutic tools for the treatment of cancer.[70] Naïve MSCs have been demonstrated to exhibit the inherent ability of blocking growth of various tumors.[71] Vegh and co-workers were the first to report the effect of PMSCs on attenuating tumor growth in 2013.[72] In vivo studies in a rat mammary cancer model demonstrated a migration and engraftment of i.v. injected PMSCs accompanied with an inhibition of the growth of primary tumors.[72]

Alshareeda et al. examined the effect of CV–MSCs in a triple negative breast cancer cell (TNBC) line, MDA MB 231.[73] This study demonstrated that CV-MSC treatment reduced proliferation, migration, angiogenic, and vasculogenic ability of TNBC cells. Additionally, treatment of cancer cells with CV-MSCs significantly decreased expression of IL-10, IL-12, CXCL9, and CXCL10 on CV-MSCs in comparison to untreated CV-MSCs. The aforementioned cytokines and chemokines have been established to play an integral role in promoting tumor cell proliferation, angiogenesis, and metastasis via immunosuppression in cancer progression.[74] Hence, this data suggest that CV-MSCS can also communicate with cancer cells and modulate its own

cytokine secretion correspondingly to cause a decrease in proliferation, migration, and vasculogenic capacity of TNBC cells.

Although the mechanism underlying the ability of PMSCs to intrinsically inhibit various tumors has not been completely elucidated, this effect can be attributed to paracrine signaling via MSCs secretions and through communication between MSCs and tumor cells.[75] MSCs secrete many cytokines, chemokines, and growth factor, which play a critical role in local cellular functions.[63] These molecules have established anti-apoptotic and regenerative capabilities.[64] Several studies have established that human MSCs inhibited growth of cancer cells (e.g., MCF-7, K562, and C6) via secretion of Dickkopf-1, which induced suppression of Wnt signaling.[76] hMSCs have also been shown to exert inhibitory effects on tumors primarily through direct contact by hindering Akt phosphorylation.[77] Consequently, there are a myriad of factors that work synergistically to induce inhibitory effects on tumors.

Nonetheless, some studies have displayed contradictory results indicating that MSCs from perinatal sources can in fact promote tumor growth.[78] A recent study by Meng et al. demonstrated that conditioned media of PMSCs from the AM stimulated proliferation of both lung and gastric cancer cell lines.[78b] Importantly, this study confirmed the promotion of tumor progression in both in vivo cancer models upon the subcutaneous co-injection of PMSCs and cancer cells.[78b] Another recent study established that both UC-MSCs and its derivatives considerably enhanced growth of lung adenocarcinoma in mice model via increased proliferation and decreased apoptosis of cancer cells.[78a] Whilst accruing studies demonstrated a correlation of PMSCs and its derivatives to tumor growth, the underlying mechanism is still unclear.

These conflicting data regarding pro versus anti-tumorigenic outcomes of PMSCs in cancer are possibly due to various reasons including the different animal models (immunocompromised vs immunocompetent) utilized in study which can elicit dissimilar immune responses which can impact tumor development.[79] Also, various experiment parameters including differing ratios of PMSCs to cancer cells being injected, timing, and route of delivery and varying types of cancer cells employed in in vivo studies may influence the outcome of study.[80] The recent preclinical studies detailed here underscores the plasticity and dichotomy of PMSCs from various perinatal tissues. Whilst PMSCs have been reported to exhibit both anti- and pro-tumorigenic behaviors, at this present stage, it is still unclear which activity prevails. Hence, further comprehensive studies need to be performed to delineate factors that impact PMSCs treatment in cancer development. PMSCs have also been exploited as potential vehicle for the delivery of chemotherapeutic drug paclitaxel (PTX) in cancer.[81] This study demonstrated the successful priming and loading of PTX in PMSCs with sustained release over time resulting in a dose dependent and enhanced killing of human pancreatic adenocarcinoma cell line in comparison to PTX treatment only.[81] This data suggest that PMSCs can be potentially utilized as carriers for the delivery of cytotoxic agents to tumors. Conversely, to date, the potential therapeutic effects of these PMSCs have yet to be explored extensively in various disease models including cancer. In contrast, the inhibitory effects of BM-MSCs and ESCs on a variety of cancer models have been demonstrated in numerous studies.[77]

3.5. Clinical Application in COVID-19 Patients

On 11th March 2020, COVID-19 was acknowledged as a pandemic by the World Health Organization. This worsening global situation has motivated many researchers to assess various treatment strategies to tackle this disease. Presently, there is no specific and effective treatment for this condition. Nonetheless, PMSCs have been employed to improve immune facilitated exacerbation in patients infected with COVID-19.[82] In chronic COVID-19 infected patients, an accumulation of pro-inflammatory cytokines leading to a cytokine storm affects those with underlying conditions as it further deteriorates their immunological mechanism system leading to death. PMSCs can block ACE-2 and TMPRSS-2 receptors and inhibit further entry of virus into the pulmonary alveolar cells.[83] Consequently, PMSCs reduces inflammation, augments immunomodulation, and result in the regeneration of compromised alveolar cells.[83]

Whilst there are 24 registered clinical trials (**Table 3**) employing the use of PMSCs derived from extraembryonic tissues for COVID-19 patients, there are only 3 completed study with highly promising reported outcomes. One of the trials involved a Phase 2 study in 100 severe COVID patients with lung damage, who were administered with three doses of 4×10^7 cells/infusion.[82b] This group established an improvement in whole lung lesion volume in comparison to placebo treated patients and displayed good tolerance and safety in patients.[82b]

A follow up to this study at 3, 6, 9, and 12 months after MSCs therapy were conducted in all 100 patients and results attained of the 1-year outcomes were recently published in January 2022.[84] Results from this long-term study demonstrated continued improvement in whole lung lesion volume and symptoms relief accompanied with no difference in adverse events reported in contrast to placebo treated patients.[84]

The second completed trial comprised of a Phase 1/2a in 24 subjects with acute respiratory distress syndrome due to COVID-19 infection.[82a] Results from this study displayed a significant increment in patient survival in PMSC treated (91%) in contrast to control treated subjects (42%).[82a] Interestingly, subjects treated with PMSCs exhibited fewer severe adverse events and decreased recovery time in comparison to control group.[82a]

Under the approval of the Chinese Food and Drug Administration (Clinical Trials Government Identifier: TS20190604404UE), a critically ill 72-year-old patient with COVID-19 induced acute respiratory distress syndrome and multiple organ damage was administered 5 infusions of 1.5×10^6 UC-MSCs kg^{-1} intravenously every 48 h.[85] MSCs treatment resulted in an increase in lymphocytes accompanied with improvement in renal and respiratory function. Whilst the patient died due to transplant rejection, MSCs therapy may be utilized as an adjunct therapy to delay worsening of COVID-19 patients with acute respiratory distress syndrome and multiple organ failure, giving them more time to receive a suitable lung donor for organ transplant.[85]

Consequently, further studies are required to ascertain effects of treatment in reducing mortality and long-term adverse effects in patients with COVID related lung damage.

Currently, a continuing Phase II clinical trial (NCT04389450) study employs the use of PMSCs administered intramuscularly in 140 patients with chronic COVID-19. This study will monitor patients for 4 weeks post injection of cells and assess efficacy of

Table 3. Registered clinical trial studies employing the use of placenta derived MSCs for the treatment of COVID-19 patients.

Identifier	Source of MSC	Status	Phase	Treatment summary	Target number of subjects	Outcome measures
NCT04288102	UC-MSCs	Completed with results	2	Three IV doses of 4×10^7 kg^{-1} cells were administered (day 0, day 3, and day 6)	100	Subjects treated with PMSCs showed improvement in whole lung lesion volume from baseline to day 28 in comparison with the placebo treated group. Overall, treatment was safe and well tolerated.[82b]
NCT04355728	UC-MSCs	Completed with results	1/2a	Two intravenous infusion of 100×10^6 cells were administered (day 0 and day 3)	24	Patient survival was significantly improved in the PMSCs versus control group: 10/11 (91%) versus 5/12 (42%) respectively. Only 2/12 subjects experienced serious adverse events after PMSC treatment.[82a]
NCT04333368	UC-MSCs	Completed with results	2b	Three IV doses of 10^6 kg^{-1} cells were administered	45	Ratio of arterial oxygen partial pressure to fractional inspired oxygen did not change significantly between MSCs versus placebo treated patients. Repeated UC-MSCs infusions were not correlated with any serious adverse effects during treatment or after.[86]
NCT04389450	P-MSCs	Active	2	Two intramuscular doses of cells will be administered (day 0 and day 7).	66	Assess number of ventilator free days and mortality of patients in 1 month.
NCT04339660	UC-MSCs	Recruiting	1	1×10^6 kg^{-1} cells will be administered in a single IV dose.	30	Assess immune function, blood oxygen saturation mortality of patients in 1 month.
NCT04490486	UC-MSCs	Recruiting	1	Two IV doses of 10×10^7 kg^{-1} cells will be administered (day 0 and day 3).	21	Assess safety of treatment, symptomatic improvement, and mortality of patients.
NCT04252118	UC-MSCs	Recruiting	1	Three IV doses of 3×10^7 kg^{-1} cells will be administered (day 0, day 3, and day 6).	20	Assess improvement of pneumonia, adverse effects of treatment, and mortality of patients in 1 month.
NCT04416139	UC-MSCs	Recruiting	2	1×10^6 kg^{-1} cells will be administered in a single IV dose.	10	Assess functional respiratory and cardiac changes. Evaluate effect on blood count, immunological cells, and safety of treatment.
NCT04313322	WJ-MSCs	Recruiting	1	Three IV doses of 1×10^6 kg^{-1} cells will be administered (day 0, day 3, and day 6).	5	Improvement of clinical symptoms. Side effects measured by chest X-ray and clearance of virus (negative test)
NCT04429763	UC-MSCs	Not yet recruiting	2	110^6 kg^{-1} cells will be administered in a single dose.	30	Assess effect on the clinical progression and mortality of patients.
NCT04273646	UC-MSCs	Not yet recruiting	1	Conventional treatment plus four IV doses of 0.5×10^6 kg^{-1} cells will be administered (day 1, day 3, day 5, and day 7).	48	Assess improvement of pneumonia and mortality of patients.
NCT04390152	WJ-MSCs	Recruiting	1	Two IV doses of 5×10^7 kg^{-1} cells will be administered.	40	Assess safety of treatment and mortality of patients.

therapy through study outcomes based on the number of ventilator or ventilator-free days and mortality rates in patients. This is an ongoing trial and is anticipated to be completed by end of September 2021.

4. Challenges for Clinical Translation

Whilst previous reported studies have displayed superior characteristic of PMSCs in comparison to its other adult counterparts in terms of enhanced immune modulation, higher expansion capabilities, and broader differentiation potential, information on various PMSC sources (DP, UC, etc.) from the placenta are not well explored. Comprehensive comparative studies in regard to inherent properties of PMSCs between different origins of placenta need to be carefully assessed and classified. For example, PMSCs from fetal origin demonstrated enhanced immunomodulation in comparison to PMSCs from maternal origin, hence may be more apposite for a specific therapeutic application. Therefore,

this raises the query regarding the ideal source of MSCs from the placenta in view of the dissimilarity in specific vital intrinsic MSC characteristics.

Whilst the utilization of PMSCs for therapeutic application has garnered interest with growing number of studies, clinical employment of PMSCs is still in nascent stage. Thus, several pertinent issues need to be addressed. First, a systematized MSC isolation technique needs to be adopted for large scale expansion in clinical trial studies to avoid ambiguity in results acquired. Advantageously, the placenta is a reservoir of MSCs which exhibit enhanced expansion potential and long-term proliferation in comparison to BMSCs.[15,24b] Additionally, Timmins and group established a large-scale process whereby a single term placenta can generate 7000 clinical doses of therapeutic MSCs.[87] Hence, these features render the placenta a clinically relevant source of tissue for the manufacture of allogeneic MSCs for the treatment of many patients.[15,87]

Studies investigating the risk and safety are of primal importance in any cell therapy. Consequently, patients with prior renal issues were presented with thromboembolism after PMSC infusion.[88] Whilst the patients were treated and cured after, this incident highlighted caution that PMSC therapy may result in prothrombotic occurrence which may result in unfavorable outcome.[88] Therefore, it is clear that long term studies are required to thoroughly evaluate any adverse effects associated with PMSC therapy.

A recent meta-analysis study from 62 randomized clinical trials reported nine serious adverse events that developed after MSC treatment which included death, infection, diarrhea, central nervous system disorders, arrhythmia, urticaria/dermatitis, vascular disorders, fever, and localized injection site adverse events.[89] Nonetheless, this analysis ascertained that MSC administration was not directly nor significantly correlated to these serious adverse events due to its low odds ratio value in all above mentioned events except for transient fever.[89] Furthermore, this analysis established no clear evidence that MSCs implantation resulted in tumor development in subjects. It should be noted that analysis from this study did not compare the effects of MSCs treatment from various tissue sources.

Interestingly, an analysis of 178 registered clinical trials and published studies between 2007 and 2017 that have adopted specifically UC-MSCS treatment revealed that only 20% of these trials have published data. Hence, it is difficult to clearly delineate the success rate of MSC therapy. Consequently, out of these, only 18% reported safety and 74% exhibited improvement in comparison to controls or expected outcome in treated subjects.[90] Another analytical study established that only 4% of published stem cell clinical trial data disclosed negative or harmful results of treatment.[91] Consequently, underreporting of clinical trial results and the predisposition whereby clinical trial outcome with positive results having a higher chance of publication in comparison to data with negative results is very concerning as it may provide a heightened expectation of treatment efficacy. Therefore, regulations should be implemented whereby it is made mandatory to publish or report all results of the clinical trial regardless of the study outcome.

5. Conclusion

MSCs have invoked a great hype for the treatment of various diseases. Whilst BM-MSCs are the most extensively studied source of MSCs, several drawbacks are involved in the application of BM-MSCs which can incumber its long-term clinical translation. Hence, the placenta represents an alternative and rich source of allogeneic MSCs which is sustainable for clinical applications. Moreover, PMSCs possess superior inherent features in comparison to BM-MSCs, which includes accessibility, higher expansion proficiencies, phenotypic plasticity, heightened immunomodulation, and lower immunogenicity which renders PMSCs more appealing for clinical translation. Due to their unique inherent characteristics, PMSCs have been investigated as a treatment tool in various preclinical and clinical studies. Nonetheless, further comparative studies of MSCs isolated from different parts of the placenta must be investigated to distinguish advantages, drawbacks, and associated adverse effects of MSC from various placental origin. These data may provide a clear elucidation to match appropriate clinical applications accompanied with reduced adverse events to the different types of PMSCs.

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Conflict of Interest

The authors declare no conflict of interest.

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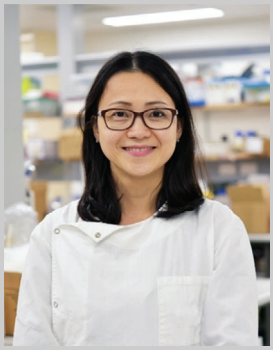

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