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Placenta-derived cells: A new source for regenerative medicine application

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ABSTRACT
The placenta is the first and most important organ of pregnancy. It is the communication bridge between the mother and fetus. Placental elements, due to their important position and function, are specially designed to manage the exchange of nutrients and the local regulation of the maternal immune system. The development of cells such as cytotrophoblasts, syncytiotrophoblasts, extravillous trophoblasts, placental giant trophoblasts, placental macrophages, and placenta-derived mesenchymal stromal cells is described. Medical researches have been performed to demonstrate the curative potential properties of these cells, such as treating burns, tendon and joint diseases, lung diseases, blood and bone marrow diseases, and other diseases. This review provides an overview of the formation and development of placental cell lines and their potential for regenerative medicinal research and ongoing clinical applications.
Keywords: Placenta, Placental MSC, Application, Clinical trial

1. INTRODUCTION

The placenta is a temporary fetal organ formed first during gestation [1]. The term placenta refers to a disc-shaped structure, 15 to 20 centimeters wide, 2 to 3 centimeters thick, and about 1/6 of the fetal weight, usually about 450 grams [2]. With a multicellular barrier structure, the placenta plays a crucial role in exchanging metabolism, oxygen provision, endocrine, and immune regulation between the mother and fetus [1, 3]. Obstetric complications consisting of preeclampsia, stillbirth, and recurrent miscarriages have been reported to be associated with placental anomalies [4]. The structure of the placenta is a parallel integration of two types of cells, including mother cells derived from the endometrium and fetal cells [5]. Five days after fertilization, the trophoblast covering the inner cell mass is formed as an outer layer of the morula, a part of which continuously develops into the placenta [1]. In preimplantation, essential transformations occur, including inner cell mass restructuring into the epiblast and primitive endoderm [5]. The amnion forms from the epiblast and merges with the trophoblast to become the amniotic chorionic membrane [5]. The embryo and the surface epithelium conjugation happens on the sixth or seventh day after fertilization [5]. The fusion of cytotrophoblast cells in the trophoblast creates the syncytium anchoring the blastocyst within the uterine walls called syncytiotrophoblast [1, 6]. Primary chorionic villi structure is formed by syncytiotrophoblasts enclosing cytotrophoblast cells penetrating the decidua basalis [6, 7]. The development of the invasion of mesoderm-derived cells creates cavities inside the tubular primary villi, forming the secondary chorionic villous structure [8]. The secondary chorionic villus impetuously ramifies and deeply invades basal decidua, then covers up the lacunae to create an intervillous space. The lacunae formation occurs due to the lytic action of syncytiotrophoblast's secretions, which degrades the matrix of the endometrium and the uterine capillaries, leading to maternal blood leakage [1, 6, 7].

During the first trimester, the invasion occurs through extravillous trophoblasts entering the decidua's nearest organ, produced by the decidualized endometrium [9, 10]. Nutritional requirements are a prerequisite for successful parity [4].

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Extravillous trophoblasts invade maternal spiral arteries, adhere to the lumen, induce endothelial cell apoptosis, and replace them [11, 12]. At the end of the invasive process, the structure of the maternal spiral artery becomes a wide tube, leading to an increase in the volume of maternal blood flow into the intervillous space [13]. The speed and volume of maternal blood flow into the intervillous space is perfectly regulated to balance the sufficient nutrient supplement. This regulation is necessary for a healthy pregnancy [14, 15]. In this review, the components of the placenta and therapeutic properties of these components in regenerative medicine are introduced.

2. PLACENTA-DERIVED CELL TYPES

Cytotrophoblast and syncytiotrophoblast

The structure of the villus that develops from trophoblasts plays a crucial role in the fetal and the maternal metabolism, allowing for successful gestation [16]. At the third week of gestation, two populations of cell types are differentiated from trophoblast, consisting of cytotrophoblasts (CTs), which are incomplete differentiated cells, and syncytiotrophoblasts (SCTs), which are complete differentiated cells [17]. As mentioned, the SCTs are created from the conjugation of the CTs, forming the villous trophoblasts which enhances the embryo's infiltration process [6, 7]. The SCTs are responsible for the bidirectional transport of nutrients and wastes, producing various placental proteins and hormones for fetal growth and protecting the inner cell mass [18]. Right after the interaction between the blastocyst and uterine wall implantation, human chorionic gonadotropin (hCG) is produced by SCTs, and it is the first endocrine signal from the fetus to the mother [19, 20]. With the corpus luteum, SCTs participate in progesterone secretion at the seventh to eighth week of gestation, maintaining stability during the early stages of pregnancy [21]. Low-density lipoprotein (LDL) receptors on the SCTs surface absorb LDL from maternal circulation in the intervillous space to synthesize progesterone [22, 23] (Figure 1). The SCTs also synthesize the steroid hormone, estrogen, and human chorionic somatomammotropin (hCS) [24, 25]. The conjugation of the CTs to form the SCTs depends on the expression of connexin 43, the activity of the gap junctional intercellular communication, and the flipping of phosphatidylserine from the inner to the outer of the plasma membrane [26, 27]. Their enormous size provides perfect coverage for endothelial cells; the SCTs avoid presentation to the maternal immune system in the intervillous spaces, which are densely populated by immune cells attract a mass of concentrated immune cells. During the first trimester, the embryo faces a large portion of maternal leukocytes in decidua that statistically include decidual natural killer (dNK) cells (70%), decidual macrophages (20 – 25%), and T cells (3 – 10%) [28, 29]. SCTs are one of the extremely rare human cells that do not express human leukocyte antigens (HLA) (both of HLA class I and HLA class II), playing a crucial role in the immune modulation strategy of pregnancy [30, 31]. Moreover, the surface glycosylation patterns on SCTs also contribute greatly to maternal immune system evasion [32]. The SCTs are reported to exocytose exosomes harbouring the tumor necrosis factor-related apoptosis-inducing ligant (TRAIL) and Fas ligands, which induce the apoptosis of leukocytes [33] (Figure 2).

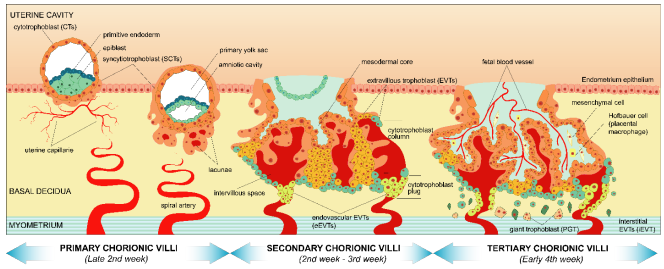

Figure 1. *The formation of the placenta.*

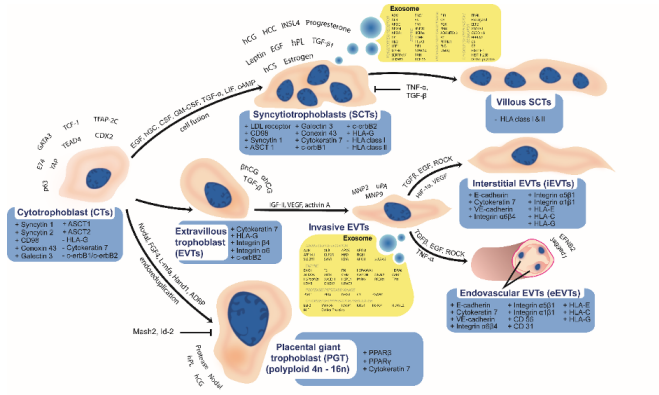

Figure 2. *The cytotrophoblast differentiation into functional cells in the placenta*

Extravillous trophoblast

The SCT-non-differentiation CTs develop into extravillous phenotypes, which further invade and form the cell column of anchoring villi [34]. A part of the CTs population differentiates into extravillous trophoblasts (EVTs) to invade decidua more effectively, and plug structures are formed by endovascular EVTs (eEVTs) to moderate the maternal blood pressure during the spiral artery invasion [35]. EVTs are also present within the myometrium, the middle layer of the uterus wall, as two cell types, including interstitial EVTs (iEVT), and placental giant trophoblasts (PGTs) [35]. The absence of local lymph nodes in the endometrium restricts dendritic cells and T effector cells and facilitates an abundance of dNK and T-reg cells [36]. SCTs and CTs are in charge of synthesizing M-CSF, GM-CSF, and IL-10, regulating the homeostatic differentiation of M2 macrophages and T-reg cells [37]. On the other hand, the EVTs secrete multiple immunoregulatory factors during invasion, such as macrophage growth factors (GM-CSF and M-CSF), cytokines (IL-1RA, IL-1β, IL-2, IL-6, IL-10, IL-17 TNF, IFN-γ, TGF-β1, TGF-cc2), chemokines (CCL2, CCL17, CCL18, CCL20, CCL22, CXCL1-3, CXCL8, CXCL10, CXCL 11), and apoptosis-inducing factor as TRAIL [37]. The EVTs present the HLA-G

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determined to interact with killer cell immunoglobulin-like receptor 2DL4 (KIR2DL4) and the leukocyte immunoglobulin-like receptor B (LILRB), which leads to the inactivation of dNK [38]. The secretion of βhCG is recorded in EVTs, and the αhCG is trivial [19]. In contrast to SCTs, EVTs predominantly produce the hyperglycosylated form of hCG, which promotes the development of the SCTs layer and angiogenesis through the LH/CG receptor [19].

Placental giant trophoblast

Placental giant trophoblasts originate from CTs through differentiation; they express the morphology of large cytoplasm and polyploidy. The first signs of primary PGTs are observed from developing the mural sixty trophectoderm cells stage. The differentiation of PGTs is carried out under stringent regulation [39]. The signal from peroxisome proliferator-activated receptor beta (PPARb) activates the Pi3K pathway; the activation of LIF is through the LIFR, starting the MAPK pathway and contributing to the formation of PGTs. Hand1 and Mash2 are crucial in PGTs differentiation and antagonization of each other [40]. Mash2 is found in the chorion, ectoplacental cone, and spongiotrophoblast, and it is responsible for maintaining these structures and the diploid stage of primary PGTs. During the PGTs differentiation, Hand1 inhibits the Mash2 activity and vice versa. The Mash2 is also controlled by the bHLH protein, I-mfa, via PPARb actions [39]. On the other hand, a dominant negative factor, Id-2, diminishes under the Pi3K pathway, leading to the act of Hand1 and the CTs to PGTs transformation. Polyploidy of PGTs is established through cell cycle alterations. In the S phase, the decrease in Geminin allows DNA replication activation, and P57kip2 inhibits the G1/S checkpoint trapping cell in the S phase [41]. In contrast, the reduction in P53 and pRB activity causes Cyclin A and E inhibition, thereby causing the S phase to maintain and repeat. At the G2 phase, p57kip2 inhibits Cdk1 function, while Snail enhances Cyclin A and B expression and allows endoreduplication to occur without mitosis [41]. The differentiation of PGTs is induced by the action of a combination of growth factors, such as EGF, TGF, IGF-I, and IGF-II, that are locally expressed in the uterus [42]. In addition to acting as EVTs, PGTs attend uterus invasion of the placenta, spiral arteries remodeling, and secretion of transcription factors, proteases, cytokines, hormones, and adhesion molecules [42].

Placenta-derived mesenchymal stromal cells (P-MSC)

The term mesenchymal stromal cells (MSC) was officially used over thirty years ago, attracting researchers for analysis and application in human disease treatment [5]. Thus far, the MSC has been isolated from many origins of human tissue and separated into two groups: adult MSC and fetal MSC. The fetal MCS is mainly identified and studied from postnatal tissue such as the placenta (P-MSC), umbilical cord, umbilical cord blood, amniotic fluid, and amniotic membrane [3]. The presence of the P-MSCs is observed around the second or third week of gestation, followed by the first fetal primitive vessel formation [17]. P-MSCs are introduced into the placenta through the mesodermal core and allocated into the placental amniotic membrane, chorionic plate, chorionic villi, chorionic leave, basal decidua, and placental blood vessels. The P-MSC has a fibroblast cell morphology and differentiates into adipocytes, osteocytes, and chondrocytes. The cells express significant membrane markers such as CD90, CD105, CD73, and lack of CD34, CD45, CD19, CD14, CD11b, CD79α, and HLA-DR [1, 5, 43]. CD44, HLA-ABC, and pluripotency markers (Rex1, Nanog, Oct4, and Sox2) are also found in P-MSCs [5]. The P-MSCs and MSCs derived from bone marrow (BM-MSC) share significant similarities [44] (Figure 3).

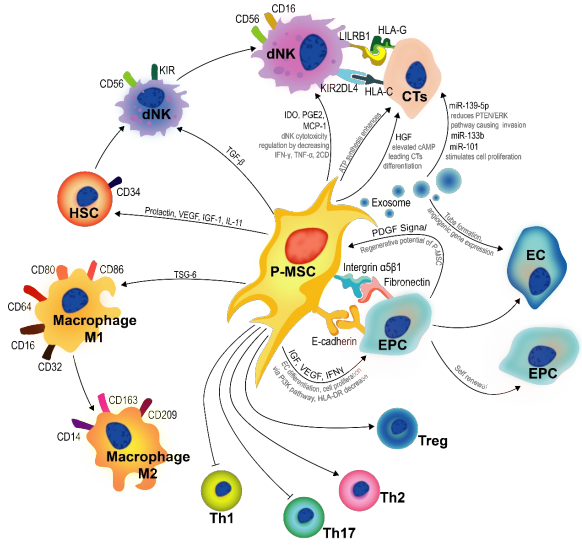

Figure 3. *The interaction of placental MSCs with other cellular components present in the placenta*

Placenta-derived mesenchymal stromal cells play a crucial role in immunomodulation at the placenta, maintaining successful gestation [3, 44]. P-MSCs enhance the hematopoietic progenitor cells, which are positive to decidual natural killer (dNK) cell differentiation from CD34 cells. dNK cells are clarified to be a majority in the decidua and account for 70% of leukocytes present in decidua [1, 5, 43]. Unlike NK in peripheral blood (pNK), the dNK cells express LILRB1, KIR2DL4, and CD56 but not CD16, exhibiting a poor cytotoxic capacity [45]. P-MSCs also secrete the TGF-β, inducing pNK to dNK phenotype conversion [45]. Moreover, the other P-MSC-derived factors, including IGF-, VEGF, IL-11, prolactin, IDO, PGE2, and MCP-1, support dNK protection and cytotoxicity regulation [42]. The interaction of dNK and CTs is determined to be intimate through the interaction of LILRB1 – HLA-G and KIR2DL4 – HLA-C [5].

In decidua, about 20 % of the leukocyte population is occupied by T cells [46]. T cell induction, proliferation, and differentiation promotion in decidua during gestation are coordinated by P-MSC, including Th1, Th17 differentiative inhibition, Th2 and Treg differentiative activation [46, 47]. Treg is active in

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decidua during pregnancy for immune response regulation [46]. Macrophages are crucial in decidua, and macrophage M2 plays a role in tissue healing and repair through anti-inflammatory processes [1]. Macrophages with the M2 phenotype, Hofbauer cells, are discovered in the chorionic villi [48]. The ratio of M1 and M2 cells balances during the initial gestation, and then the M2 polarization elevates after the mature placental formation. Previously, the M1 phenotype macrophage differentiative retardation is reported as the impact of P-MSC and its secretions [49]. The attendance of P-MSC in the co-culturing orientated the increased expression of CD14, CD163, and CD209, representing M2 phenotype as well as the inhibitory factors including B7-H4, PD-L1, and PD-L2, and the decline of CD40, CD80, and CD86 markers, and proinflammatory cytokines [46, 49].

Placenta-derived mesenchymal stromal cells participate in the development of the placenta [1]. The promotion of endothelial growth of P-MSCs is recognized through the signaling interaction of E-cadherin/beta-catenin and fibronectin/integrin α5β1 between P-MSC and endothelial progenitor cells (EPC) [50, 51]. Developing endothelial cells (EC) from EPC is augmented by P-MSC growth secretions such as VEGF and IGF [42]. In addition, the HLA-DR-expression decreases under the action of IFN-γ from the P-MSC, thereby avoiding an unwanted response from the maternal immune system [50]. The reverse interaction from EPC to P-MSC via the PDGF signaling pathway plays a role in the regenerative potential of P-MSC [1, 51]. P-MSC-derived exosomes contribute to EC cell tubule formation and the development of angiogenic factors [1]. HGF derived from P-MSC induces cAMP synthesis, activating the differentiation from CTs to SCTs. *MiR-139* influences the invasion of CTs included in P-MSC-derived exosomes, down-regulating the MAPK pathway [52]. On the other hand, *miR-133b* and *miR-101* enhance the development and proliferation of CTs and related cells [52].

Placenta macrophage (Hofbauer cell)

The Hofbauer cells (HCs) first appear at the start of the third week of gestation and remain during the pregnancy [48]. The HCs mainly reside along the walls of fetal blood vessels' placental villous core, and some of the HCs are also found in the amnion [1]. The populations of HCs are diverse, with multiple phenotypes separated by considering the surface markers such as CD163, CD68, CD64, CD14, HLA, DC-SIGN, and others [46, 49]. The expression of CD14 is the most unstable and bonds to the pro-inflammation response [46, 49]. Besides, the MHC class II positive proportion in the HCs population moves up and down during the gestation, documenting the HLA-DP and HLA-DQ elevation and HLA-DR collapses in the third trimester [48]. Based on gene expression detection, HCs display the M2 macrophage phenotype and reflect all M2a, M2b, M2c, and M2d sub-types [49]. HCs activities contribute to fetal protection [48]. The attraction of HCs is caught in villitis caused by a viral infection. Immunoregulation is one of the HCs functions through the secretions of growth factors such as VEGF, TNF, TGF-β, and several cytokines such as IL-1, IL-6, IL-10, CCL-2, CCL-18, and others. HCs derived VEGF and Spry modulate the villi branching formation [49]. Vasoregulation of placental vessels is partially regulated by prostaglandin E2 and thromboxane, which HCs secrete in *in vitro* models. HCs activate the production of hCG and hPL by CTs [46, 49]. The presence of alpha-1 antitrypsin and inter-alpha-trypsin inhibitors in HCs plays a role in protease inhibition related to villous remodeling and differentiation processes in the placenta.

3. MEDICAL APPLICATION OF PLACENTA-DERIVED CELLS

Tendon and joint disease treatment

Tendon and joint disease is a common pathology, especially from the beginning of middle age, such as tendinopathies (43%), musculoskeletal pain (21%), Achilles tendinopathy (11%), and others [53]. Non-steroidal anti-inflammatory and corticosteroid drugs or physical treatments are used for various tendon and joint diseases [53]. However, the persistent symptoms of the condition are not easy to eliminate [54]. Placental-derived elements promise a new, effective therapy for tendon and joint disease treatment [55]. The extract from the placenta is proven to be diverse in nutrient and regular factors [56]. Tendon injury caused by collagenase has been shown to heal rapidly under the impact of cells isolated from the placenta, which actively increases the secretion of IL-1β and IL-6 during the treatment [49]. P-MSC activity is involved in tendon repair only through enhancing skeletal muscle regeneration and preventing muscle atrophy [1]. P-MSCs have a role in extracellular matrix remodeling and a central role in local immune regulation [1]. The MSC and tenocyte interaction has still not been completely understood, but the promotion of M2 cell phenotype polarization and IL-4 secretion are likely to play a role in the treatment of tendon and joint disease through the extracellular matrix (ECM) remodeling [49]. Besides, promoting the vascular proliferation of MSCs in the tendon injury model has also been described [56]. In a previous clinical study, P-MSC was also considered a benign therapeutic agent as there were no abnormal symptoms observed, such as biochemical and hematologic disadvantages, ectopic tissue or tumour formation, pulmonary embolism, and liver or renal impairment in patients for 24 weeks post-treatment [57].

Erectile dysfunction treatment

The erection of the penis depends on the volume of blood present in the cavernous body [58]. Under conditions of sexual stimulation, acetylcholine interacts with muscarinic receptors, stimulating increased intracellular free Ca^{2+} ions and activating endothelium-derived nitric oxide synthesis [59]. An increase in nitric oxide activates soluble guanylate cyclase, leading to the rise in cGMP, which causes a decrease in intracellular Ca and relaxation of cavernous smooth muscle and facilitates penile erection [59]. Peyronie's disease is a condition in which fibrotic structures form hard plaques when the penis is erect, causing curvature, deformity or erectile dysfunction [60]. Thus far, scientific studies have indicated that injection of P-MSC improves

Peyronie's disease [61]. The efficacy and safety of microinjection of P-MSC in Peyronie's disease is undergoing phase 1 clinical trials (ClinicalTrials.gov number NCT04771442) in cases of penile curvature of 15 – 90 degrees and fibrous plaques on the tunica albuginea of the penis during erection. The use of P-MSC in treatment can be considered an alternative therapy instead of surgery in cases of Peyronie's disease treatment [61]. Moreover, in clinical trials on erectile dysfunction, the use of P-MSC, has also been tested (ClinicalTrials.gov number NCT02398370).

Blood and bone marrow disorders treatment

Vascular remodeling is a function of P-MSC with VEGF, HGF, and BDNF secretion [62]. Secretions from P-MSCs, including proteins and EVs, play an essential role in regenerating congenital and acquired spinal cord injuries [62]. Clinical trials such as ClinicalTrials.gov numbers NCT002688049, NCT04520373, NCT03308565, NCT02917291, NCT04213131, NCT03505034, 03521232, NCT03521336, NCT05018793 in the treatment of spinal cord injury from MSC have been created the premise for the application of MSC in orthodox medicine shortly [62]. P-MSC's angiogenesis and remodeling of the injured area's effects are believed to have suitable applications in treating myocardial injury, atherosclerosis, nerve and limb ischemia, and stroke [63, 64]. Moreover, interactions with P-MSC and immunoregulatory cells are actively involved in rehabilitating myeloproliferative disorders and other aplastic anemias [65]. The safety and efficacy of P-MSC in aplastic anemia and myelodysplastic syndromes treatment have been progressing to the second phase, which is yielding positive results (ClinicalTrials.gov numbers NCT01182662 and 001129739).

Type 2 diabetes mellitus treatment

Cell transplantation therapies in treating diabetes were first used in the early 2000s [66]. In the first cases of treatment, the source of donated cells was the deceased, and there were many limitations in the source of samples [66]. Applying P-MSC can be advantageous in terms of cell supply [67]. The differentiation process into pancreatic islet beta cells (IPCs) is dominant in treating type 2 diabetes, directly releasing insulin [68]. The control of T-cell populations by P-MSCs is essential in protecting IPCs [47]. In addition, the regeneration of IPCs is also stimulated by growth factors secreted from P-MSC, such as IGF, PDGF, and VEGF [42, 69]. P-MSC helps patients with type 2 diabetes significantly reduce insulin levels in treatment (ClinicalTrials.gov numbers NCT01413035) [70]. Other clinical and preclinical studies have also shown similar results about the effectiveness of MSCs in the treatment of type 2 diabetes with multiple effects [71].

Treatment of burns

The MSC burn wound healing process is described in several stages. The anti-inflammatory phase occurs when the immunoregulatory processes of MSCs are accomplished through the polarization of M2 cells and regulation of T cells [47]. MSC-derived exosomes release miRNAs that promote protein synthesis [72]. During the wound repair phase, growth factors are actively involved in promoting cell proliferation, regeneration of the ECM, and angiogenesis [2, 18]. Placental-derived MSCs are also a cell source of interest in treating burns. Other particular burns, such as Corneal alkali burns, are also being studied for applying P-MSC as a therapy [73].

Treatment of lung injury

After the COVID-19 pandemic, respiratory health problems are of particular concern [74]. The sequelae of Covid-19 and lung damage are significant threats to human health [74]. MSC-induced remodeling is targeted as an effective tool in remodeling damaged lungs [75]. P-MSC has been proven to treat acute respiratory distress syndrome caused by Covid-19, in which P-MSC can migrate, attach, and re-heal the injured lung tissue [76]. The mechanism of the action in the treatment lung by P-MSC is considered through the proinflammatory elements secretion, especially IL-1, IL-6, IL-12, IFN-γ, and TNF-α [77]. Macrophage immunomodulation induced by P-MSC was found to affect the LPS-induced acute lung injury model [78]. Other factors, such as placental EVs, also contribute to treating lung diseases [79].

Conclusion

The placenta was once considered a medical waste. However, with the current exploitation potential, the placenta is gradually becoming a raw material for regenerative medicine. The biological interaction mechanisms of cells of placental origin, including immunomodulatory, anti-inflammatory, EVs, and other secretory activities, are still under intensive investigation. The clinical trials that have been conducted indicate the archivable application potential of placental cells.

Compliance with Ethical Standards

Conflict of interest: The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions: NTQ, BTKL, and HTC analyzed the data. All authors wrote the draft manuscript. The authors painstakingly read and approved the final manuscript.

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