Tissue Engineering: Current Research

Chapter 3

Perinatal Stem Cells in Tissue Engineering

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Abstract

Perinatal stem cells are a class of self-renewing and heterogeneous populations derived from mother and fetus tissues with unique immunomodulation and multi-lineage differentiation potential and the concomitant regenerative medicine. To date, a variety of perinatal stem cells such as hematopoietic stem cells, mesenchymal stem/stromal cells, amniotic stem cells and subtotipotent stem cells have been identified from hematological and non-hematopoietic placental sources, which serve as particularly interesting candidates for the administration of recurrent and refractory diseases. Herein, we focus on the characterization of the biofunction, application and the underlying mechanism of placental stem cell-based tissue engineering. Furthermore, we describe the promising prospective and formidable challenges during the application of placental stem cells in the field of regenerative medicine.

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1. Introduction

Stem cells are particular population with self-renewal and multi-lineage differentiation potential, and thus acknowledged as advantaged sources for tissue engineering and regenerative medicine against recurrent and refractory diseases [1-3]. Stem cells are commonly divided into three subsets based on the origin including embryonic stem cells (ESCs), adult stem cells and perinatal stem cells [3-5]. The placenta is a temporal and functional organ between the maternal and fetal vascular beds with multiple properties and plays a pivotal role in facilitating fetal development and govern the outcome of pregnancy by immunomodulation as well as nutrient and oxygen delivery [6-8]. The "discarded" placenta acts as one of the most promising sources with a variety kind of placental stem cell generation from two counterparts of placenta (mother and fetus) such as hematopoietic stem cell (HSC), mesenchymal stem/stromal cells (MSCs), amniotic stem cells, and sub-totipotent stem cells [9-12].

For decades, substantial literatures contribute to the large-scale preparation of cell sources for regenerative medicine [4,13]. For instance, perinatal blood including cord blood and placental blood is a well-acknowledged source for HSC enrichment and the concomitant HSC transplantation (HSCT) and hematologic malignancy administration [4]. Meanwhile, the aforementioned MSCs generated from other non-hematopoietic placenta and umbilical cord tissues with unique hematological-supporting and immunomodulatory properties have been extensively investigated in advanced perinatal stem cell-based cytotherapy both clinically and preclinically [14-16].

In this chapter, we mainly focus on the state-of-the-art knowledge of perinatal stem cell-based tissue engineering from the view of biological phenotypes, biofunctions and the underlying molecular mechanism in regenerative medicine. Moreover, we also discuss the fascinating prospective and formidable challenges together with the future directions in the field of perinatal stem cell-based cytotherapy and tissue engineering.

2. Classification of Perinatal Stem Cells

2.1. Hematologic Stem Cells (HSCs)

HSCs are unique cell population with remarkable self-renewal and multiple potentiality towards functional hematopoietic cells and immune cells such as erythrocytes, white cells (e.g., neutrophils, eosinophils, basophils, lymphocytes, monocytes), macrophages, megakaryocytes and the derivatives (e.g., platelets) [17-20]. According to developmental biology, HSCs are unique subsets of endothelial cells, namely hemogenic endothelial cells, during embryogenesis [21]. As reviewed by Yuan *et al*, HSCs are one of the most well-acknowledged adult stem cells (ASCs) described with the "SMART" features including self-renewal, multi-lineage differentiation, apoptosis, rest and trafficking [22].

Based on the inherent attributes, HSCs are widely used in allogeneic transplantations for the treatment of severe autoimmune diseases, hematologic malignancies and nonmalignant diseases[23-25]. For instance, according to the American Society of Hematology (ASH) 2021 guidelines for sickle cell disease, HSC transplantation (HSCT) has been recognized as the only curative intervention for sickle cell disease (SCD) [26]. Notably, Foell *et al* verified the encouraging outcomes of SCD patients with haploidentical T-cell-depleted HSCT in children and adults [23]. Furthermore, patients are reported with better prognosis after co-transplanted HSCs with MSCs or an anti-thymocyte globulin (ATG) or other immunosuppressive agents for the rapid hematopoietic reconstitution and effective prevention of GvHD [27-29].

Distinguish those mobilized from adult peripheral blood, HSCs generated from the umbilical cord blood (UCB) and placental blood serve as preferable sources for unmanipulated haploidentical HSC preparation [28]. Of note, despite with high rates of success for various metabolic storage diseases and hematologic disorders, UCB-derived HSCs are mainly limited to children with low cell dose needs due to the limitation in yield [28, 30]. To date, HSCs have been reported successfully generated from human pluripotent stem cells (hPSCs), which thus provide alternative new cell sources for the preparation of HSCs as well as disease remodeling, toxicity screening and drug discovery *in vitro* [21,31-33].

2.2. Mesenchymal Stem/Stromal Cells (MSCs)

MSCs, also known as medicinal signaling cells or multipotent mesenchymal progenitor cells, are heterogeneous cell population with unique immunoregulatory and hematopoietic-supporting properties, together with multi-lineage differentiation potential towards adipocytes, osteoblasts and chondrocytes [34-37]. Since the year of 1968, MSCs with diverse origins have been generated from adult tissues (e.g., adipose tissue, bone marrow, dental pulp or follicle, synovium) [24, 38, 39], perinatal tissues (umbilical cord, umbilical cord blood, placental tissue, amniotic membrane or fluid) [40-42] and even differentiated from human pluripotent stem cells (e.g., embryonic stem cells, induced pluripotent stem cells) [43-45]. For example, our group recently reported the high-efficient generation of MSCs from embryonic stem cells and induced pluripotent stem cells via screening and combination of chemical small molecules [43,44].

As the uppermost stromal cells in the constructive microenvironment, MSCs play pivotal roles in physiological hematopoiesis and the concomitant hematologic malignancies [11,36, 46]. For example, Zhao and the colleagues compared the cryobiology and transcriptomic characteristics of umbilical cord-derived MSCs (UC-MSCs) at various passages and identified the conservative property in the treatment of graft-versus-host disease (GvHD) [11]. Conversely, Huo *et al* and Wei *et al* reported that bone marrow-derived MSCs (BM-MSCs) generated from patients with acquired aplastic anemia revealed multifaceted variations upon

those from healthy donors in orchestrating the subpopulation of T lymphopoiesis, together with the efficacy of UC-MSCs or VCAM-1^+ MSCs upon the corresponding disease model [42, 46].

Distinguish from those derived from adult tissues and pluripotent stem cells, perinatal stem cells such as UC-MSCs and placental-derived MSCs (P-MSCs) have been demonstrated with preferable characteristics in long-term *in vitro* proliferation and immunomodulation, together with remission of ethic risk and etiological risk [11,42,45]. Considering the robust superiority, MSCs generated from perinatal tissue serve as splendid alternative cell sources for tissue engineering and regenerative medicine [15,47].

2.3. Amniotic Stem Cells

Amniotic membrane is a unique construction and highly abundant tissue, which thus acts as a splendid source and attractive material for stem cell isolation such as amniotic epithelial cells (AECs) and amniotic mesenchymal stem cells (AMSCs) [48]. In details, AECs and AMSCs are respectively isolated from embryonic ectoderm and embryonic mesoderm, which possess similar immunophenotype whereas manifest differences in multipotential towards mesodermal lineages [49].

Amniotic stem cells are generated from perinatal amniotic membrane with low immunogenicity and anti-inflammatory capacities, and capable of promoting migration and adhesion of epithelial cells and the resultant tissue engineering [50, 51]. For instance, Cetinkaya-Un *et al* reported the alleviative effect of AMSCs upon X-irradiation-induced testicular damage via suppressing endoplasmic reticulum stress and apoptosis [52].

2.4. Sub-totipotent Stem Cells

Sub-totipotent stem cells, also acknowledged as MSC system, are left-over cell population during embryonic development, which are considered as the top of a hierarchical system in post embryonic development. As a hypothesized undefined subfraction of embryonic-like stem cells, sub-totipotent stem cells are available to generate derivatives with similar phenotypic biomarkers for clinical applications [53,54].

The post-embryonic sub-totipotent stem cells are composed of all MSCs, which thus possess the multifaceted characteristics including multilineage differentiation, paracrine and autocrine (e.g., cytokines, anti-inflammatory factors, chemokines, micro-vesicles, exosomes), low immunogenicity, and functional microenvironment [11,54]. For instance, bone marrow-derived $Flk1^+CD31^-CD34^-$ MSCs of sub-totipotent stem cells have been demonstrated with differentiation potency towards to produce osteoblast, hepatocyte-like cells, islet-like pancreas cells, neuron and endothelial cells at single-cell level [54].

3. Regulatory Mechanisms of Perinatal Stem Cells

To date, perinatal stem cells, including the hematologic and non-hematologic counterparts, have been extensively explored in a variety of disease treatment, and in particular, the intractable relapsing and refractory diseases by orchestrating a series of regulatory mechanisms [55-58]. Generally, MSCs function via an elaborate orchestration of mode of action such as differentiation, secretion (e.g., autocrine, paracrine), bio-directional immunomodulation [59, 60].

3.1. Direct- and Trans- Differentiation

As mentioned above, HSCs can differentiate into hematopoietic progenitor cells and the resultant functional blood cells and immune cells, which thus play a pivotal role in hematopoietic homeostasis and immunologic homeostasis [61, 62]. Similarly, MSCs identified from non-hematologic perinatal tissue have been reported with multi-lineage differentiation potential towards functional tissue cells (e.g., chondrocytes, vascular endothelial cells)[42, 54]. For instance, Hou *et al* took advantage of P-MSCs with dual-fluorescence expression for the treatment of refractory Crohn's-like enterocutaneous fistula in mice, and verified the spatio-temporal distribution and therapeutic mechanisms of P-MSCs via accelerating neovascularization and downregulating ROS [15].

3.2. Autocrine and Paracrine

Perinatal tissue-derived MSCs fulfil a predominant characteristic in constructing an advantageous microenvironment critical to hematogenesis and pregnancy [63]. Of the mode of action, secretion including autocrine and paracrine plays a core role in intercellular communications between MSCs and the adjacent damaged tissues or cells, which is the cornerstone of MSC-based cytotherapy and tissue engineering for regenerative medicine [15, 64].

To date, a variety of secreted substances by perinatal stem cells have been consecutively identified including exosome, micro-vesicles (MVS), cytokines and anti-inflammatory factors (e.g., VEGF, IL-6, IL-8, IL-10, PGE-2, HGF, SDF-1) in the cultural supernatant. For instance, exosomes containing microRNAs, circRNAs and proteomes have been put forward by numerous talented investigators in the field and manifest robust prospective in preclinical and clinical practice [9, 65-67]. For example, Loy *et al* recently reported the therapeutic implications of UC-MSC exosomes and conditioned medium in attenuating influenza virus-associated acute lung injury (ALI) [68]. Instead, Del Fattore and the colleagues demonstrated the different effects of MSC-derived extracellular vesicles (MSC-EVs) upon U87MG glioblastoma cells and thus held the prospective for delivering antiblastic drugs [69].

Nevertheless, before large-scale application in clinical application, multidimensional improvement should be improved to overcome the inherent disadvantages and risks of perinatal stem cells, and in particular, perinatal tissue-derived MSCs with low-efficacy in exosome release, heterogeneity, rapid degradation and clearance [70-73].

3.3. Bidirectional Immunomodulation

Of perinatal stem cells, MSCs-derived from different counterparts (e.g., UC-MSCs, P-MSCs, AMSCs) revealed splendid characteristics, and in particular, the high cellular vitality and bidirectional immunomodulatory effect [11,74]. Extensive literatures have indicated the secretion of multiple anti-inflammatory factors involved in immunomodulation and the resultant tissue engineering, including the aforementioned interleukin family (e.g., IL-2, IL-6, IL-8), angiopoietin-1, stromal cell-derived factor 1 (SDF-1), transforming growth factor (TGF), keratinocyte growth factor (KGF), and vascular endothelial growth factor (VEGF) [42, 75-79].

For decades, perinatal stem cells have been reported with therapeutic effect upon immune diseases such as graft-versus-host disease (GvHD), atopic dermatitis, allergic rhinitis, urticaria, pediatric asthma, systemic lupus erythematosus (SLE), immunologic thrombocytopenic purpura [11,80, 81]. For instance, mast cells with pro-inflammatory factor expression have been considered playing a critical role in numerous autoimmune processes and allergic reactions, which can be effectively reversed by systemic MSC administration [82,83]. Simultaneously, perinatal tissue-derived MSCs have also been indicated in the administration of intractable disorders including diabetic nephropathy, aplastic anemia, chronic obstructive pulmonary disease (COPD), acute myocardial infarction (AMI), COVID-19 induced acute lung injury/acute respiratory distress syndrome (ALI/ARDS) via suppressing cytokine release syndrome (CRS) and improving the microenvironment to reduce lung epithelial cell damage [11, 46, 59, 76, 84-88].

4. Perinatal Stem Cell-based Tissue Engineering

Perinatal tissues such as cord blood, umbilical cord, placenta, placental blood and amniotic membrane are advantaged sources for perinatal stem cell generation as well as tissue engineering and regenerative medicine[6-8]. For example, Xin *et al* took advantage of a collagen scaffold laden with UC-MSC-derived exosomes (CS/Exos) for the treatment of intrauterine adhesions, and verified the therapeutic effect including promoting fertility restoration and endometrium regeneration via facilitating anti-inflammatory responses and improving macrophage immunomodulation[89]. Yea *et al* combined UC-MSCs with a biomimetic hydroxyapatite-gradient (HA-G) scaffold for the rotator cuff repair by ameliorating the damage of tendon-to-bone interface (TBI), and found that collagen organization and cartilage formation were respectively improved by 52% at 8 weeks and 262.96% at 4 weeks compared to the repair group [90].

As to osteoarticular disorders, Chung *et al* compared the therapeutic effect of various hydrogels/UC-MSCs composites upon rats with articular injury including alginate/UC-MSCs, chitosan/UC-MSCs, pluronic/UC-MSCs, hyaluronic acid (HA) /UC-MSCs. With the aid of multifaceted measurement indicators, they verified that HA/hUC-MSCs rather than the relevant hydrogel composites resulted in achieved cellular arrangements and collagen organization pattern much similar to those adjacent uninjured articular cartilages [91]. Furthermore, Tang and the colleagues verified that small extracellular vesicles (sEVs) derived from UC-MSCs (UC-MSC-sEVs) showed comparable therapeutic effect for osteoarthritis (OA) with UC-MSCs, whereas with upregulated proteins associated with immune effector process, extracellular matrix (ECM) organization, Rap1 and PI3K-AKT signaling pathways instead [92].

Taken together, the encapsulated MSCs or other counterparts of perinatal stem cells as well as derivatives (e.g., sEVs, exosomes) in combination with injectable hydrogels or relevant biomaterials have attracted considerable attentions in recurrent and refractory disease management attributes to their advantaged chondrogenic differentiation capacity [93-95].

5. Clinical Trials of Perinatal Stem Cell-based Cytotherapy

During the past years, perinatal stem cell-based cytotherapy has caught the attention of biologists and clinicians in the field for tissue engineering and regenerative medicine. According to the Clinicaltrials.gov database of National Institutes of Health (NIH), a total number of 10 clinical trials has been registered worldwide (up to May 23th, 2022) such as China, United States, Netherlands, France and Mexico (**Figure 1**). The interventional studies initiated by clinical investigators are aiming to explore the safety and effectiveness of MSC-based remedies for relevant disease treatment (Figure 1). Of the aforementioned clinical trials, 1 was withdraw or recruiting, 2 were not yet recruiting, 4 were completed, and 2 were unknown status (**Table 1**). Meanwhile, we noticed that most of the registered clinical trials were in the Phase 1 and/or Phase 2 stage(s) except 2 trials were unknown instead (**Table 1**).

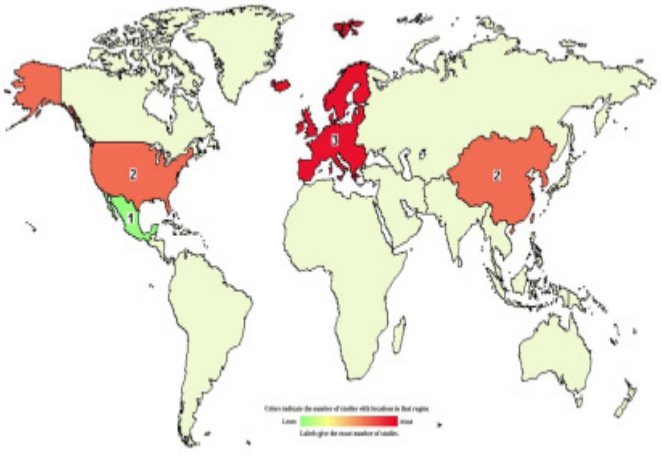

Figure 1: Illustration of perinatal stem cell-based clinical trials.

Table 1: Perinatal stem cell-based clinical trials.

NCT No.	Status	Phases	Enrollment	Locations
NCT02772289	Completed	Phase 2	90	Maternal and Child Health Hospital of Foshan, China
NCT04034615	Recruiting	Phase 2	90	Maternal and Child Health Hospital of Foshan, China
NCT03356821	Completed	Phase 1, 2	10	Wilhelmina Children's Hostpital/University Medical Center Utrecht, Netherlands
NCT01700166	With-drawn	Phase 1	0	Children's Memorial Hermann Hospital; University of Texas Health Science Center - Houston, United States
NCT01284673	Completed	-	10	Assistance publique Hopitaux de Marseille, France
NCT02881970	Unknown status	Phase 1, 2	20	Assistance Publique Hopitaux de Marseille, France
NCT03760900	Completed	Early Phase 1	15	-
NCT01506258	Unknown status	-	20	Neonatology Department of the Pediatrics Service, Hospital Universitario Dr. Jose E. Gonzalez, Mexico
NCT04798716	Not yet recruiting	Phase 1, 2	55	Mission Community Hospital, United States
NCT03899298	Not yet recruiting	Phase 1	5000	-

According to the ClinicalTrials.gov website, 10 perinatal stem cell-based clinical trials were intuitively displayed (up to May 23th, 2022).

6. Prospective and Challenges

Perinatal tissues are "discarded" medical wastes for the huge quantity of hematopoietic and non-hematopoietic stem cell generation for tissue engineering. Considering the special structure between mother and fetus, perinatal stem cells are splendid "seeds" that manifest low immunogenicity, robust proliferation, and immunoregulatory attributes. However, there's still a long way before the large-scale application in regenerative medicine and new drug application (NDA). Firstly, despite perinatal stem cells and the concomitant derivatives (e.g., exosome, sEV) have emerged as promising alternatives for relapsing and refractory disease administration and tissue engineering, yet the continuous optimization of interventional remedies is still urgently needed to fulfil the aims such as safety, effectiveness, repeatability and cost-effective for clinical practice. Secondly, for the large-scale preparation of the homogenous and clinical-grade perinatal stem cells, the GMP-compliant cryopreserved master cell bank and the standardized preparation technology are of equal importance and urgently needed such as culture materials, conditions (e.g., culture medium, supplements, relative humidity, the concentration of CO_2 and O_2), technologies and manipulations[96]. Thirdly, extensive literatures have suggested that MSC-encapsulated biomaterial scaffolds (e.g., HA, nHAP, PLGA) exhibit increased cell vitality with prolonged curative effect and decreased apoptosis as well as enhanced multi-lineage differentiation potential, yet the systematic and detailed characterization of the biofunction and underlying mechanism are still far from satisfaction. Overall, in the context of tissue damage and intractable disorders, perinatal stem cells with

multifaceted opportunities and challenges are recognized as promising “off-the-shelf” product in the next-generation cytotherapy and tissue engineering by targeting recurrent and refractory diseases.

7. Acknowledgment

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