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Perinatal tissues and cells in Tissue Engineering and Regenerative Medicine

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Abstract

Perinatal tissues are an abundant source of human extracellular matrix proteins, growth factors and stem cells with proved potential use in a wide range of therapeutic applications. Due to their placental origin, these tissues possess unique biological properties, including being angiogenic, anti-inflammatory, anti-fibrotic, anti-microbial and immune privileged. Additionally, as a temporary organ, placenta is usually discarded as a medical waste, thus providing an easily available, cost effective, 'unlimited' and ethical source of raw materials. Although some of these tissues, such as the amniotic membrane and umbilical cord, have been used in clinical practices, most of them continue to be highly under explored. This review aims to outline the most relevant applications of perinatal tissues as a source of biomaterials and stem cells in the exciting fields of tissue engineering and regenerative medicine (TERM), as well as highlight how these solutions can be used to overcome the shortage of adequate scaffolds and cell sources that currently hampers the translation of TERM strategies towards clinical settings.

1. Introduction

The human body has a limited ability to efficiently repair and regenerate damaged tissues after an injury or medical disorder affect them. For this reason, when an organ starts to fail or completely loses its function, the standard therapy is to replace it by a functional organ or tissue which has been extracted from the own patient or donated by a compatible donor. However, organ and tissue transplantation continue to be largely hampered by the lack of suitable donors as well as the frequent occurrence of severe immune responses that lead to graft rejection. Tissue engineering and regenerative medicine (TERM) have therefore emerged as an innovative and multidisciplinary field that combines cells, biomimetic matrices and signalling factors to replace or restore the normal biological function of tissues (Figure 1). Despite the great advances made in recent years, the search for adequate cell sources and suitable biomaterials continues to be a focus for TERM researchers. [1] [2]

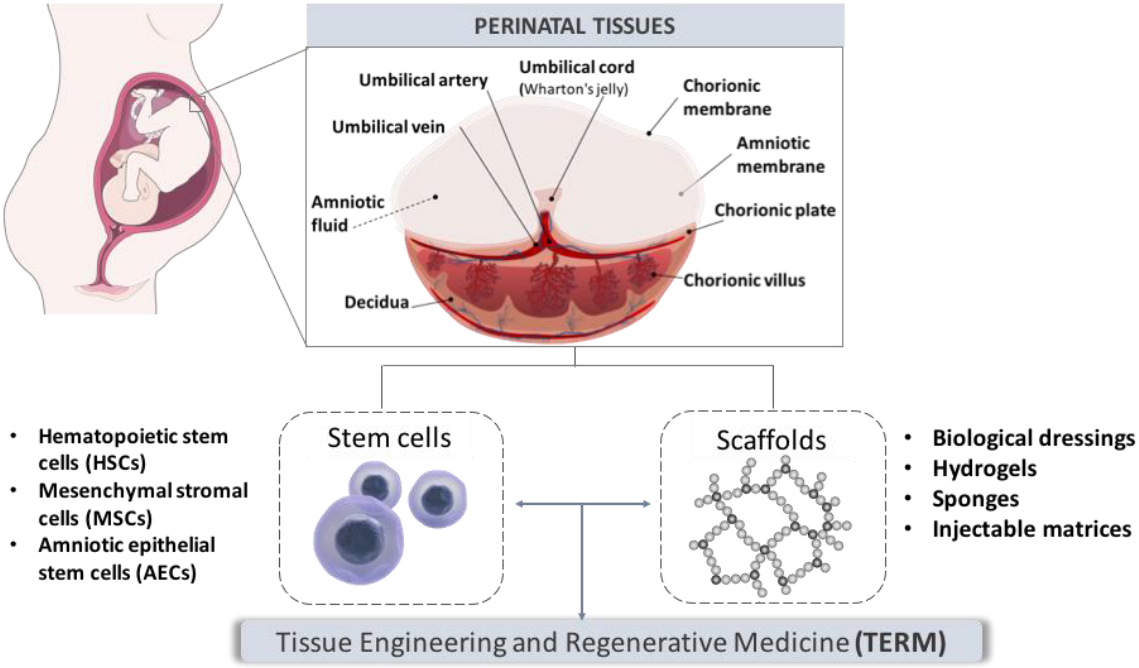

Figure 1: Schematic representation of perinatal tissues currently used for cell isolation and biomaterials fabrication for applications in TERM.

In real wound healing processes, a blood clot forms to provide physical support for the restoration of the tissue. Also scaffolds have been designed to support tissue regrowth, but with the additional purpose of stimulating and guiding regeneration so that a new, completely functional tissue is formed at the end of the healing event. To achieve this goal, biomaterials from both natural and synthetic origin have been developed which intend to recreate the cells' native microenvironment by providing them with key biochemical and mechanical cues. However, while synthetic materials frequently fall short of the necessary complexity, the natural ones rarely derive from human sources which limits their clinical application. [3] [4] [5, 6] In this context, some recent works have been focused on the development of human based materials for TERM applications. [7] [8] [9] Also stem cells, which play a pivotal role in the formulation of TERM strategies, have been mainly focused on embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and adult derived stem cells, especially those derived from bone marrow (BM-MSCs) and adipose tissue (ASCs). However, while the procurement of ESCs requires the destruction of the human embryo therefore being frequently linked to ethical and safety concerns, iPSCs might be associated with higher occurrence of epigenetic and genetic aberrations raising safety concerns regarding their use in humans. The utilization of adult MSCs has been limited by the invasiveness of the harvesting procedures and the senescence of cells related to the donors age. [10] [11] Perinatal

tissues possess numerous types of stem cells that exhibit properties of both embryonic and adult stem cells, that make them attractive candidates for TERM. It was on this scope that perinatal tissues started to be investigated as an abundant source of human-derived biomaterials and cells that hold the potential to overcome most of the obstacles currently imposed by available technologies and produce the next-generation of bioengineered therapies [12] [13] [14].

Placenta is a unique temporary organ that forms during pregnancy to ensure fetus nourishment and development as well as prevent immune rejection (Figure 1). According to this biological function, tissues isolated from term placentas have demonstrated to retain important therapeutic properties, which mostly result from anti-microbial, anti-inflammatory and immunomodullatory activities of resident cells [15]. Besides, as a medical waste these tissues can be readily use in clinical and commercial settings as safe and cost-effective solutions to current TERM strategies. Remarkably, whereas some of these tissues, especially the amniotic membrane and umbilical cord, have been used in clinical practices for over a century, others, such as the chorionic membrane, have only been subject of intense research in recent years [12]. Here we review and discuss the advances that have been done regarding the use of perinatal tissues and derived stem cells in the exciting field of TERM. Perinatal derived materials currently on the market are also featured in this review.

2. Perinatal Tissues

2.1. Amniotic membrane

During pregnancy, fetus and amniotic fluid are involved by a fetal membrane responsible not only to protect them but also for allowing the exchange of nutrients and metabolic products with the maternal body. Amniotic membrane (AM) is the innermost part of the fetal membrane that directly contacts with the embryo and aids its normal development by preventing mother's immune rejection and microbial contaminations [16] [17]. AM is a thin, translucent tissue composed of a single epithelial layer, a thick basement membrane and an avascular stroma that retains exceptional mechanical and biochemical properties with proven clinical value.

In the first years of its use, fresh human AM was clinically applied as a graft or biological dressing for the treatment of dermatological and ophthalmologic defects, such as wounds [18], burns [19] and non-healing ulcers [20]. Since then, the introduction of improved processing and preservation techniques has expanded the applicability of AM-based biomaterials to more complex conditions, including organ and tissue regeneration (e.g.

oral cavity, bladder [21], bone [22], and ocular surface [23] [24]). Currently, commercial products from human AM (e.g. AmnioGraft® and MiMedx®) are already routinely marketed as effective tools for the treatment of conjunctival disorders (e.g. restrictive strabismus) and regeneration of damaged tissues (e.g. wounds) owing this tissue' innate ability to enhance wound healing, reduce scarring and inflammation, and prevent microbial infections. (Table 1) Although the therapeutic behaviour of AM is still not fully understood, the accumulation of anti-inflammatory cytokines (interleukin (IL)-10 and IL-1 receptor antagonist), antimicrobial peptides (β-defensins, elafin) and tissue inhibitor of metalloproteinases (TIMP-1, 2, 3 and 4) on the tissue extracellular matrix (ECM), and their slow release after implantation is a well-accepted explanation [25] [26]. Moreover, several other paracrine factors are thought to be involved by supressing pro-inflammatory cytokines (IL-6 and IL-8), immune cells (T cells, B cells and dendritic cells) and chemotactic activities of macrophages and neutrophils that are typically recruited during host's immune and inflammatory responses [27] [28]. For example, the heavy chain–hyaluronic acid/pentraxin 3 (HC-HA/PTX3) complex, recently isolated from cryoperserved AM, was considered critical to this anti-inflammatory, anti-scarring and anti-angiogenic actions by inducing apoptosis of activated neutrophils and macrophages, enhancing phagocytosis of apoptotic neutrophils by macrophages, and reducing macrophage infiltration, while promoting their polarization towards M2 phenotype [29] [30].

Equally important for the clinical success of AM-based biomaterials is the fact that amniotic cells do not express human leukocyte antigen (HLA) -A, -B and –DR, but produce immunosuppressive cytokines (e.g. IL-4, IL-10), thus contributing to the low immunogenicity, and consequent exceptional biocompatibility, of the material upon *in vivo* implantation [27] [31] [32]. Regarding the wound healing capacity, it was demonstrated that AM reduces fibrosis by downregulating some members of the transforming growth factor beta (TGF-β) superfamily, including TGF-β1 and TGF-β2, while expressing TGF-3β [33]. Recently, it was also discovered that AM promotes re-epithelialization of tissues by stimulating the migration of specific cells, such as keratinocytes, at the front edge of wounds [34]. This is mainly achieved by the presence of paxillin and focal adhesion kinase, two proteins greatly involved in the regulation of focal adhesions via c-Jun N-terminal kinase (JNK) and Mek-Map kinase signalling pathways. Collectively, these findings suggest that AM may promote regeneration not only by providing a physical support for tissue ingrowth but primarily by releasing paracrine factors necessary for wound healing and tissue ingrowth, thus resulting in the formation of a new, scarless tissue structurally and functionally similar to the original.

Although human AM has been used in clinical practice for many years, its application as an engineered biomaterial is relatively recent. To date, several works confirmed that AM matrix contains multiple components that make it an attractive starting material for the formulation of scaffolds, including key structural proteins (e.g. collagen type I, III, V, VI, fibronectin and laminin) and growth factors [35] [36]. It was on this scope that researchers started to explored it as a multipurpose substrate that served either as i) a pre-clinical tool for investigation purposes, for example on stem cell and cancer research [37] [38], ii) a carrying matrix for the local delivery of cells on cell-based therapies [39] [40], or iii) a tissue engineered construct for tissue or organ repair [41] [42].

Indeed, one popular strategy in TERM involves the use of scaffolds as temporary matrices to promote *in situ* tissue regeneration. Decellularized AM has demonstrated to be a suitable scaffold for the *ex vivo* expansion and delivery of cells, specially stem and progenitor cells. For example, limbal epithelial stem cell sheets are frequently transplanted into patients suffering from limbal stem cell deficiency, a condition that results in loss of corneal clarity, conjunctivalization, and visual loss. Although it is a proven efficient method to restore the corneal epithelium, it sometimes fails due to the low regenerative potential of cells within the limbal sheet, as a result of the loss of proliferative capacity and stemness during expansion [43] [44]. De-epithelized AM is able to enhance the growth and stemness of limbal epithelial sheets in explant culture as was demonstrated by the increased expression of limbal stem cell markers, indicating higher proliferative and regenerative capacity [39]. Remarkably, Shang et al. have recently developed an ultra-thin AM, by removing some of the stroma with collagenase IV, that is optically clearer that previous scaffolds, therefore promoting the formation of more transparent and thicker cell sheets [40].

Another common application of de-epithelized AM is in the culture of allogenic skin cells to create skin substitutes that could repair critical defects, such as non-healing wounds or severe burns [41] [42]. Wilshaw et al. were the first demonstrating the ability of acellular AM to support the attachment, proliferation and viability of human primary keratinocytes and fibroblasts during *in vitro* culture. This work also highlighted the potential clinical use of these skin substitutes by proving their *in vivo* biocompatibility after implantation on a mouse subcutaneous model. Results showed that explanted AM was extraordinarily well integrated into the host tissue, and promoted rapid infiltration of host cells without inducing an immune response (low number of T cells) or calcification [45]. These results were recently corroborated by a phase I clinical trial where the safety, feasibility and potential efficacy of human AM was evaluated in burn patients. The results revealed faster healing times and lower pain intensity on patients treated with AM when compared to controls (placebo-treated) [19].

The cumulative evidences that human AM can be successfully used as a skin substitute have recently inspired the development of novel AM-based biomaterials for skin TERM. For instance, Gholipourmalekabadi et al. reported the development of a three-dimensional (3D) bi-layer scaffold made of decellularized AM with nanofibrous of silk fibroin on top, which improved the mechanical properties of the material [46]. The scaffold not only supported the attachment and proliferation of adipose tissue-derived MSCs (AT-MSCs), but also promoted the expression of important pro-angiogenesis factors. These results suggest that enhancing the mechanical properties of the AM, either by crosslinking or combination with other materials, may be a promising strategy to increase the value of the scaffold for TE approaches. Remarkably, Ji et al. also developed an innovative biomaterial consisting of 3D micronized AM which was able to quickly amplify ESCs expansion *in vitro* while retaining an undifferentiated phenotype [47]. When tested in *in vivo*, it successfully carried cells into the injured site and promoted wound regeneration, as was evidenced by the formation of a new epidermis and dermal layer. The authors emphasize that the similarities between the scaffold microenvironment and the stem cell niche within the human body are not only favourable for the *ex vivo* expansion of stem cells but can also be used to regenerate tissues *in vivo.*

In the past few years, decellularized AM has also attracted attention as a potential carrying matrix for MSCs. As previously mention, MSCs are important for cellular therapies applied to cardiovascular diseases, spinal cord injuries, bone and cartilage repair and autoimmune diseases. However, while their systemic delivery can cause side effects resulting from poor biodistribution and retention in kidneys and lungs, their local injection requires large amounts of cells that very often end up being released into the bloodstream. The development of adequate substrates to deliver MSCs directly into target tissues is therefore of paramount importance to increase the success rate of these strategies.

To date, both decellularized and non-decellularized AM have been successfully used to support the attachment and proliferation of BM-MSCs without causing cytotoxic effects [48]. In addition, these scaffolds have been used to support differentiation of MSCs towards specific cell lineages, as a strategy to regenerate different tissues. For instance, Naseer et al. reported the potential of decellularized AM basement membrane to support proliferation and differentiation of umbilical cord-derived MSCs (UC-MSCs) and placenta-derived MSCs (P-MSCs) into chondrocyte-like cells [49]. Khorramirouz et al. also demonstrated the ability of decellularized AM to support AT-MSCs differentiation into cardiomyocytes when applied as a cardiac patch for the treatment of acute myocardial infarction in rat models [50]. This study further confirmed the potential of AM-based scaffolds as support and delivery matrices for cardiac neovascularization and regeneration. Using a different strategy, Chen et al. utilized

decellularized AM seeded with BM-MSCs and endothelial progenitor cells to successfully repair a 3-cm circumferential urethral defect in dogs [51]. Here, the AM provided an even distribution of the stem cells, stimulated tissue regrowth and epithelization, and avoided ischemia. Alternatively, Ryzhuk et al. developed a hydrogel from decellularized AM which was suitable for the culture of BM- and P-MSCs as well as other commonly used cell lines (C2C12 and SH-SY5Y) [52]. This type of scaffold can significantly enhance the utility of the AM as a platform for cell therapy, as hydrogels can be easily injected to deliver cells locally without the need of invasive procedures. Hydrogel biomaterials have been widely used as 3D substrates for *in vitro* culture of cells due to their structural similarity to soft tissues [53]. The use of human derived substrates, in particular, AM-derived ECM to create these hydrogels is therefore a major advance which promises to more faithful reproduce the native microenvironments of the human body *in vitro* comparing to commonly used materials sourced by animal tissues, such as Matrigel® or collagen.

Although most of the studies employing human AM for TERM are focused on the regeneration of soft tissue, such as skin, cornea and cartilage, some groups already started to investigate its feasibility for stiffer tissues, like bone. Indeed, Chen et al. studied the effects of an acellular AM matrix on the osteogenic differentiation of MSCs and concluded that both sides of the scaffold can be used to potentiate the induction effect of osteogenic supplements [54]. In another study, Lindenmair et al. demonstrated that AM can be differentiated in toto (i.e. without native cells removed) under osteogenic conditions to produce scaffolds for bone TE [55]. The osteoblastic differentiation of amniotic epithelial stem cells (AECs) and amniotic membrane-derived MSCs (AM-MSCs) was confirmed by the expression of specific markers, such as osteocalcin, alkaline phosphatase and bone morphogenetic proteins (BMPs). Notably, this novel 'in toto' differentiation approach can be used to produce scaffolds with increased functionality, since viable cells continue living in their native microenvironments therefore avoiding the stress caused by isolation, culture and re-seeding procedures. In fact, the same group already used this strategy to produce scaffolds for peripheral nerve [56] and cartilage [57] TE both with promising results.

Table 1. List of commercial companies dedicated to the development and commercialization of biological scaffolds derived from perinatal tissues.

Company	Product	Product description	Application

Celularity, Inc.	Biovance®	Decellularized, dehydrated AM	Wound healing
MiMedx Group, Inc.	AmnioFix® EpiFix® EpiBurn®	Dehydrated AM/CM	Wound healing
	AmnioCord® EpiCord®	Dehydrated UC	Connective tissue regeneration
Amnio Technology, LLC	AmnioFill®	Acellular placental tissue	Connective tissue regeneration
	PalinGen®	Amniotic tissue	Connective tissue regeneration
	Flow™	Air dried AM	Wound healing
	InovoFlo™	Amniotic fluid components	Wound healing
Amniox Medical Inc	NEOX® Clarix® Cord	Cryopreserved UC/AM matrix	Wound healing
	NEOX® Clarix® FLO	Lyophilized UC particulate	Wound healing
	NEOX® Clarix®100	Cryopreserved AM matrix	Wound healing
	RESPINA®	Cryopreserved AM	Adjunctive treatment for spine surgery
Surgenex, LLC	SurFactor®	Injectable acellular AM	Protective cushion
	SurForce®	Concentrated and cryopreserved AM	Protective cushion
	SurGraft®	Dehydrated AM	Protective covering
	SurCord®	Concentrated and cryopreserved UC	Protective cushion
Ventris Medical, LLC.	Cellesta™	AM sheet	Wound healing
	Cellesta™ Flowable	AM suspension	Protective cushion
	Cellesta™ Amnion Granulate	AM particulate	Wound healing
Skye Biologics Inc.	ActiveBarrier®	AM or AM/CM	Wound healing
	ActiveMatrix®	Flowable placental tissue	Wound healing

CryoMatrix®	Cryopreserved flowable placental tissue	Wound healing
BurnMatrix®	High Volume Placental Tissue matrix	Burn healing
WoundEx®	Dehydrated AM or AM/CM	Wound healing
PTM Therapy®	Complete placental connective tissue matrix	Connective tissue regeneration
ReVive™ Membrane	Dehydrated placental membrane	Wound healing
ReVive® Flow	Complete placental connective tissue matrix	Rejuvenation therapy
OculoMatrix® VisiDisc®	Dehydrated AM Dehydrated AM/CM	Ocular tissue repair

2.2. Chorion

Several groups reported the development of biomaterials composed of both fetal membranes (amnion/chorion) which have been used for wound healing, bone [58] and vascular [59] TERM research. Indeed, the company MiMedx® developed various products consisting of dehydrated human amnion/chorion membrane that have been used as bioactive allografts to reduce scar tissue formation, modulate inflammation, enhance healing, and act as barrier membranes in several conditions, including burns and non-healing wounds (e.g. diabetic foot ulcers and venous leg ulcers) [60] [61]. In addition to the good results obtained as a skin substitute, these products have also demonstrated the ability to recruit stem cells to the wound site, *in vitro* and *in vivo,* as well as modulate their responses in order to produce key soluble signals, including regulators of inflammation, mitogenesis, and wound healing [62]. These findings were recently corroborated by the work of Massee et al. where soluble extracts of dehydrated human amnion/chorion membrane were able to modulate the behaviour of AT-MSCs *in vitro* by stimulating their migration, proliferation, and cytokine expression, favouring the expression of signals that may accelerate diabetic wound healing[63].

Although few works report the use of chorion alone to produce scaffolds, it seems that this membrane can be used to fill some gaps existing in AM-based TERM. One of the fields where the chorionic membrane (CM) could have advantages over AM is in bone TE as is evidenced by the growing number of works using amnion/chorion scaffolds for this purpose

[58] [64] Besides, it was recently suggested by Go et al. that extracts from CM significantly enhance the osteogenic differentiation of MG-63 cells compared to extracts from AM [65]. This is probably a result of differences in the composition of these two materials, especially with regard to osteogenesis-related growth factors, such as basic fibroblast growth factor (bFGF), TGFβ-1, and epidermal growth factor (EGF). The results of this study strongly suggest that CM can be used as a therapeutic material for bone regeneration in contrast to other ECM-based materials which are mostly used for regeneration of soft tissues.

2.3. Placenta

The placenta, composed of the chorionic plate (fetal side) and decidua (maternal side), is another example of a perinatal tissue that has received little attention in past years. However, this is also a rich source of ECM proteins and growth factors which has the additional advantage of being highly vascularized, thus holding great potential to be applied in vascular TERM or in the development of large tissue constructs.

One of the first works describing the use of the whole placenta as a scaffold for TE, developed a personalized perfusion system to efficiently decellularize isolated cotyledons and large segments of tissue by injecting the required chemicals via the existing vasculature [66] [67]. Although good decellularization efficiency was achieved, the resulting material was unable to support the long-term survival and proliferation of adipose precursor cells. In an attempt to optimize this system, the authors developed a composite material composed of placental acellular matrix and crosslinked hyaluronan. Once again, the placental matrix facilitated the cellular attachment and spreading but did not proved to be useful as a scaffold for adipose TERM [68]. Alternatively, Choi et al. used decellularized placentas to produce ECM sheets that successfully retained key ECM components and growth factors, including TGF-b1, bFGF, EGF, platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF), therefore providing appropriate scaffolds for skin regeneration [69]. Indeed, the placenta-derived sheets displayed good integration when implanted *in vivo*, promoting migration of keratinocytes and epithelial cells, as well as neovascularization. In addition, the presence of this scaffold facilitated wound closure leading to the formation of a new skin with similar structure to the natural one. In another study, Rameshbabu et al. also demonstrated that hybrid ECM sponges of placenta and silk fibroin can provide a suitable microenvironment for growing human foreskin fibroblasts, human epidermal keratinocytes and human AM-MSCs *in vitro*, therefore serving skin TERM purposes [70]. When implanted in full-thickness wounds in a rat model this

scaffold also favoured wound healing with the formation of a stratified skin tissue and pronounced neovascularization. Placenta based hydrogels prepared by a straightforward process of decellularization followed by an enzymatic treatment and gellification at 37°C have also proved its efficacy in treating cardiac ischemia damage in animal models [71].

These results suggest that placenta-derived scaffolds may be more appropriate for wound healing than for adipose TERM, probably due to the presence of important growth factors and cytokines prominently involved in the regeneration of skin tissue.

Rameshbabu et al. also investigated the potential of using placenta-derived sponges for osteochondral TERM [72]. They successfully demonstrated that this scaffold was able to support the growth of AM-MSCs *in vitro*, as well as their differentiation into chondrogenic and osteogenic lineages under induction. Moreover, after being subcutaneously implanted, the scaffold did not provoke severe immune responses, supported the formation of blood vessels and promoted osteochondral regeneration. Once again, the presence and retention of key bioactive molecules, such as BMP-4, TGFβ1, VEGF and placental growth factor (PLGF), known to be involved in bone, cartilage and blood vessel regeneration, may explain the positive outcomes when using placenta for TERM strategies. The work of Moore et al. strongly corroborates these findings by demonstrating that placenta-matrix derivations can be used to stimulate angiogenesis and/or vascularization when applied as a coating or angiogenesis modulator [73]. In fact, the described material contains human-derived molecules at near physiological ratios which suggests that it can be used to induce and model angiogenesis more efficiently than previously used approaches, including the "gold standard" Matrigel® and single or discrete combinations of angiogenesis modulators. Moreover, it also contains immune related and basement membrane proteins considered important for this type of application. Therefore, it can serve not only for TERM purposes, for example to improve the biocompatibility and integration of a biomaterial, but can also be used as an angiogenesis model for clinical and pharmaceutical applications, for example to test the efficiency of specific drugs. To explain the good results obtained, both *in vitro* and *in vivo*, the authors suggested that the numerous growth factors and cytokines present on the matrix, which include angiogenin, hepatocyte growth factor (HGF), FGF-4, leptin, intercellular adhesion molecule (ICAM)-1, ICAM-2 and TIMP-2, can resemble the broad set of molecular interactions occurring *in vivo* therefore stimulating the various metabolic pathways required for the formation of new vessels.

The promising results achieved so far will certainly motivate future works to develop placenta-derived biomaterials for TERM applications, especially as a strategy to induce vascularization during tissue regeneration or artificial tissues production.

2.4. Umbilical cord

The umbilical cord (UC) is the structure that connects the developing embryo to the placenta, thus ensuring the continued supply of nutrients and oxygen to the fetus during pregnancy. For such, UC comprises two umbilical arteries and one umbilical vein, through which deoxygenated and oxygenated blood are carried out, respectively. Surrounding and protecting the umbilical vessels is Wharton's jelly (WJ), a mucoid connective tissue mainly composed of collagens (I, III and VI) and glycosaminoglycans, especially hyaluronic acid. Additionally, it also contains various important growth factors, including aFGF, bFGF, IGF-I, EGF, PDGF and TGF-β1 [74] [75] [76].

Although current research has been mainly involved in isolating stem cell populations from the UC, this tissue has long been explored as a source of grafting materials for TE [77] [78] [79]. Indeed, one research focus has been the use of UC veins and arteries to produce tissue-engineered vascular grafts that could overcame the limited number of autologous vessels available for replacement of diseased segments in cardiovascular diseases. For such, researchers are using decellularization techniques to obtain structurally and mechanically functional vessels that can be re-cellularized with appropriate cells, such as endothelial, progenitor and myocardial cells. For instance, Gui et al. proposed the decellularization of an umbilical artery to prepare a 3D scaffold with similar mechanical properties to the original vessel, which supported the formation of a confluent endothelial layer *in vitro* [80]. When implanted *in vivo* as an abdominal aorta interposition graft in a nude rat, it was able to withstand the natural forces imposed without collapsing. These results suggest that UC arteries may be a suitable alternative to commonly used grafts, which include autologous vessels, artificial materials and glutaraldehyde cross-linked umbilical veins. In another study, Daniel et al. demonstrated that by defining appropriate protocols to produce decellularized UC veins, these scaffolds can also be used as functional vessels that support the growth and migration of cells, therefore facilitating their integration with the host tissues while minimizing the risks of graft failure [81]. Alternatively, Hoenicka et al. suggested the application of UC veins as “living scaffolds”, meaning that they are preserved intact, with the cellular components on, to be later used as functional grafts [78]. Once preserving both smooth muscle cells and endothelial cells during cryopreservation seems not possible to achieve, they suggested that retaining a functional layer of ordered smooth muscle cells would keep the vasomotoric function of the vessel, whereas the endothelial function could be restored by seeding isolated endothelial cells. Although the results have not been entirely

positive, the idea of using all the components of an UC vein to produce functional scaffolds for TE applications could be a good strategy for future works.

Recently, researchers started to propose using UC veins for other TE applications rather than as a vascular graft. For instance, Abousleiman et al. investigated the potential of decellularized human umbilical vein to be used as a scaffold material for musculoskeletal soft tissue regeneration [82]. The idea was to take advantage of the longitudinal mechanical properties of the umbilical vein to engineer artificial tendons and ligaments with comparable mechanical strength to their counterparts. For such, they cultured MSCs on the luminal side of the decellularized graft and demonstrated that it was capable of supporting cell integration, proliferation and migration. Moreover, enhanced mechanical properties were recorded after two weeks of culture suggesting that seeded cells were able to remodel the existing matrix as well as to deposit new one. In another study, Chan et al. also investigated the potential of decellularized umbilical vein as an allogeneic scaffold for engineering the vocal fold lamina propria [79]. In this case the umbilical vein was dissected with WJ on the abluminal surface and re-seeded with human vocal fold fibroblasts from primary culture. Similar to results of the previous work, fibroblasts rapidly attached and migrated into the scaffold and started to synthetize new matrix proteins. These findings highly support the use of human umbilical vein on the production of scaffolds with potential to serve not only vascular TE approaches, but also for other tissues' regeneration. WJ has also attracted great attention of TE researchers, especially because it contains high contents of ECM proteins and growth factors important for the success of cell seeding, tissue integration and, most importantly, tissue regeneration. Some of the components that have been demonstrated to be key on WJ composition are hyaluronic acid, which is known to interact with the cluster of differentiation (CD) 44 expressed in multiple cell types, including MSCs, and peptide growth factors, such as IGF-1 and PDGF, which play a role in controlling cell proliferation, differentiation, synthesis and remodelling of the extracellular matrix [74]. The work of Jadalannagari et al. was one of the first to demonstrate that WJ can be efficiently decellularized while retaining important ECM proteins [83]. The produced scaffold was biocompatible and supported the attachment, proliferation and migration of both WJ- and BM-MSCs without signals of lineage commitment. When implanted in a murine bone defect model, the decellularized WJ potentiated host osteocytes migration into the matrix suggesting good integration and cell attraction properties. Moreover, the porosity, elasticity and compressibility of the material make it easy to configure in irregular or curved shapes, thus facilitating its application as a scaffold for bone and cartilage defects. Alternatively, decellularized WJ can be processed to produce sponges that could facilitate its use as a skin substitute in full thickness wounds.

Beiki et al. demonstrated that WJ-based sponges were able to improve attachment, penetration and growth of fibroblast and enhance the wound healing process without excite inflammatory responses [84].

Following the trend of the past few years, various studies also reported the solubilization of whole UC as a strategy to produce scaffolds with distinct properties [76] [85]. For instance, Kočí et al. investigated the potential use of whole UC to produce injectable scaffolds for neural tissue repair. For such, common protocols of decellularization and solubilization, using an enzymatic solution were applied and a biocompatible, self-assembling hydrogel was obtained. These features are critical for the development of appropriate materials that can be applied for neural and other soft tissue reconstruction. Remarkably, when injected into a rat model of photothrombotic lesion, the UC hydrogel was densely infiltrated by resident macrophages, predominantly M2-like phenotype, hence suggesting constructive host tissue remodelling rather than deposition of dense connective tissue and scarring. Safari et al. used a similar strategy to produce scaffolds from whole UC, but instead of an injectable hydrogel they developed a sponge-like structure with suitable properties (e.g. porosity and mechanical properties) for cartilage TERM [85]. This type of construct was able to support BM-MSCs attachment and proliferation, as well as aid the formation of a cartilage-like tissue and the biosynthesis of collagen after chondrogenic induction. Collectively these findings encourage future investigation on the use of the UC as a raw material to create valuable constructs which could be applied in multiple TERM applications, and possibly find translation to clinical settings.

3. Perinatal stem cells

3.1. Hematopoietic stem cells (HSCs)

Hematopoietic stem cells (HSCs) are the cells involved in haematopoiesis, the process by which all mature blood cells are produced. This means that HSCs have the capacity to differentiate into all blood cell types, including white blood cells, red blood cells, and platelets. Moreover, HSCs are multipotent and the ability for self-renewal which make them an attractive source of cells for TERM [86]. In the human body they are primarily found in the bone marrow (BM) and rarely on the peripheral blood [87]. Additionally, they can also be found on blood from newborn's UC and placenta [88]. Thus, collection and banking of UC derived cells have become a popular option for use in cell therapies

In previous years, BM was considered the main source of HSCs for clinical application. However, the intricate harvesting of BM from donors has hampered the routinely and prompt

utilization of this source. Alternatively, UC blood appears as a promising, readily-available source of HSCs which does not require invasive harvesting strategies. For this reason, UC blood has been used in cellular therapies to treat several disorders affecting the hematopoietic system, such as leukaemia and Wiskott-Aldrich syndrome, and to help regrow healthy blood cells after chemotherapy. Recently, clinical trials involving UC blood transfusions into children with autism also yielded promising results in the preliminary phase I, which included improvements in speech, socialization, and eye contact [89].

Although UC-HSCs transplantation have demonstrated to be superior to standard BM transplantations in terms of ease of harvesting, donor match facility and immune rejection, it is important to note that smaller amounts can be collected from a single UC, which may be not sufficient to treat an adult patient. To overcome this limitation, dual-cord blood transplantations are currently being tested [90]. Alternatively, cell culture techniques that allow the *ex vivo* expansion of cells from UC blood are also under investigation, which intend to increase the number of HSCs that can be obtained from each sample [91] [92]. However, since recreating stem cell niches, particularly the hematopoietic niche, at the laboratory remains a great challenge to biology and biomaterials researchers, most of these studies continue to fail in arresting cells in an undifferentiated state for long periods, hence frequently resulting in mature rather than immature cells [93].

Understanding the mechanisms that regulate HSCs fate and choosing the right *ex vivo* cell culture conditions have therefore been intense areas of research in recent years [93]. Strategies to re-create the HSCs niche *in vitro* primarily included the supplementation of culture medium with cocktails of cytokines, growth factors and small molecules known to influence HSCs behaviour *in vivo* (e.g. IL-3, IL-6, IL-9, thrombopoietin and stem cell factor) [94]. Afterwards, researchers started to target signalling pathways commonly involved on HSC cell fate determination, such as the Notch [95] [96], wingless and JNK pathways [97] [98] More recently, co-cultures with non-hematopoietic cells and the use 3D platforms produced from natural and synthetic materials have also emerged as promising strategies to improve UC-HSCs expansion and homing.

The BM-hematopoietic niche is a unique 3D microenvironment that regulates HSCs self-renewal and proliferation as well as differentiation. For this reason, it has been meticulously used by researchers as a template to create valuable environments *in vitro* [99]. One of the elements that compose these niches and directly influences HSCs behaviour are MSCs. Indeed, the use of feeder-layers of MSCs during *ex vivo* expansion of HSC has demonstrated to significantly improve their expansion by modulating cell-to-cell communications and secreting specific cytokines that are involved in the maintenance of self-

renewal and stemness [100]. Moreover, co-culture and co-administration of these two cell types have been shown to promote a more efficient engraftment of HSCs in mice and fetal sheep models, as well as reduce the risk of graft-versus-host diseases in transplanted patients due to the immunomodulatory activity of MSCs [92]. These findings were recently corroborated by a clinical trial (NCT00498316) where UC-HSCs expanded *ex vivo* with MSCs were transplanted into patients that received myeloablative therapy [101]. They observed that this strategy shortened the time to cumulative incidence of neutrophil and platelet engraftment, therefore concluding that it resulted from an increased number of committed myeloid and megakaryocytic progenitors that were capable of rapid engraftment after transplantation. Other cell types have been demonstrated to play a role in hematopoietic niche and positively influence HSCs expansion during co-culture experiments, including osteoblasts [102] and MSCs-derived osteoblasts [103], and perivascular-related cells (e.g. perivascular nestin-expressing MSCs, CXCL12-abundant reticular cells and semi-immortalized transfected human umbilical vein endothelial cells) [99] [104].

Although soluble signals and neighbouring cells are critical on hematopoietic niches, there are other cues equally important in the regulation of cell behaviour that still under investigated, namely the 3D environment that composes the BM. It was in this scope that 3D scaffolds capable of support HSCs expansion *in vitro* for research and clinical applications started to be developed. One of the first works reporting the use of a 3D scaffold to culture HSCs used Cytomatrix, a biocompatible 3D carbon matrix coated with the metal tantalum, to successfully expand these cells without the need of cytokines [105]. Later, Leisten et al. demonstrated that collagen-based scaffolds were also able to expand HSCs with the additional advantage of recapitulating the two distinct niches that occur within living tissues [106]. In fact, two sub-populations of HSCs were formed during the experiment, as a result of the presence of a suspension and a migratory phase. While HSCs in suspension are highly proliferative and have tendency to lineage commitment, migratory HSCs expressed clonal expansion and an immature CD34+ CD38− phenotype with self-renewal and repopulation capacity. This study highly evidences the importance of having a supporting matrix to re-create specific niche features that otherwise were not possible.

With the recent advances in the field, and taking into account the increasing interest and rapid development of areas like TERM, new and more complex biomaterials started to be used in the creation of these scaffolds [107]. One good example is the work developed by Bianco et al. where a natural scaffold from decellularized bovine BM was used to co-culture HSCs and MSCs without the need of exogenous factors [108]. Results revealed that cells were able to repopulate the BM and MSCs started to produce important chemoattractants that

could possibly favour the long-term culture of HSCs. In a similar study, decellularized WJ matrix was used to co-culture HSCs and MSCs, but this time MSCs did not positively impact the culture [77]. However, the decellularized tissue demonstrated to be a promising scaffold for the expansion of HSCs by maintaining HSC primitive phenotypes and supporting their potential for lineage differentiation and transmigration. Several other culture systems have been under investigation as potential *in vitro* environments for the efficient expansion of HSCs which could boost the clinical use of these cells.

3.2. Mesenchymal stromal cells (MSCs)

MSCs are multipotent progenitor cells that can differentiate into multiple cell types while maintaining their self-renewal capacity. In addition, MSCs possess immunosuppressive and antimicrobial properties that result from the release of bioactive factors, such as TGFβ-1, prostaglandin E2, nitric oxide, IL-6 and β-defensines, which make them attractive candidates for the treatment of conditions involving autoimmune and inflammatory components (e.g. graft-versus-host disease) [109] [110]. Although BM-MSCs are currently the "gold standard" source of MSCs for pre-clinical and clinical applications, some limitations related to painful harvestings, low isolation yields, donor age-related cell senescence and limited *in vitro* expansion and differentiation efficiency, have motivated the search for alternative sources either in adult (adipose, muscle and connective tissue) or perinatal tissues (amniotic fluid, placenta, fetal membranes and UC) [111].

Extra-embryonic cell sources are particularly interesting as cells can be readily harvested in large numbers using non-invasive strategies and without fostering typical ethical concerns (since it is a material usually discarded). To date, several cell populations have been identified on perinatal tissues that display multilineage differentiating ability and are capable of self-renewal. This includes cells from maternal origin, such as decidua-derived MSCs [112], but especially from fetal origin including those from the chorionic villi, amnion (AM-MSCs), chorion (CM-MSCs) amniotic fluid (AF-MSCs) and umbilical cord (UC-MSCs), particularly from Wharton's jelly (WJ-MSCs) [111] [113]. Numerous studies dedicated to the characterization of these cells in terms of adherence, surface markers, gene expression profile, differentiation capacity and immunophenotype, have confirmed their mesenchymal identity [114]. In general, all these cells have the ability to differentiate towards "classic" mesodermal lineages (osteogenic, chondrogenic and adipogenic), as well as towards cell types of all three germ layers, which include ectoderm (neural), mesoderm (skeletal muscles, cardiomyocytes and endothelial) and endoderm. Moreover, similarly to BM-MSCs and AT-MSCs, they

positively express typical mesenchymal markers, such as CD90, CD105 and CD71, while being negative for hematopoietic (CD34 and CD45) and monocytic (CD14) markers [115] [116]. They also maintain a similar immunophenotype by expressing HLA class I but not HLA class II, hence favouring their use in allogenic transplantations for TE [117]. Increasing evidences also suggest that stemness, immunoregulatory, proliferative and engraftment properties may be predominantly expressed and functional on these MSCs, when compared to those obtained from adult tissues, such as BM-MSCs and AT-MSCs [118] [119].

Of special importance, several groups have confirmed the existence of MSCs in human amniotic fluid expressing the pluripotent stem cell marker Oct4. AF-MSC can give rise to diverse differentiated cells including adipogenic, osteogenic, myogenic, endothelial, neurogenic and hepatic lineages, holding thus special interest for therapeutic applications [120] [121].

The abovementioned features make perinatal tissues a promising source of MSCs for therapeutic applications. Although stem cells from UC blood and MSCs from adult origin continue to be the most applied in clinical settings, the number of pre-clinical and clinical trials testing MSCs from extra-embryonic origin has been rapidly growing. So far, preliminary studies have explored their potential in a broad range of health conditions, including neurological [122] and cardiac diseases [123], diabetes [124] [125] [126], regeneration of tissues (e.g. liver [127] [128]) and control of immune and inflammatory responses[129] [130] [131]. Additionally, perinatal cells have also been attracting attention of pharmaceutical companies. For example, Celgene Cellular Therapeutics is currently developing a cell-based therapy composed of placenta-derived adherent cells to treat autoimmune and inflammatory diseases, called PDA-001 (previously known as cenplacel-L). The cells are harvested from full-term postpartum placenta using patented procedures and administered by intravenous injection to patients. Phenotypically, they express nominal CD10+, CD105+, and CD200+ markers, moderate levels of HLA class I and undetectable levels of HLA class II, and do not express the co-stimulatory molecules CD34, CD80 and CD86 [132]. In preclinical models of neuropathic pain, experimental allergic encephalomyelitis and ischemic stroke, PDA001 consistently exhibited immunomodulatory, anti-inflammatory, pro-regenerative, neuroprotective and angiogenic properties [133] [134] [135]. For instance, Chen et al. tested the therapeutic effects of PDA001 in mice with chronic heart failure and observed significant improvements in cardiac function and fibrosis, with enhanced proliferation of endothelial cells and cardiomyocytes [133]. Importantly, this study suggests that therapeutic effects of PDA001 may result from modulatory paracrine effects rather than *de novo* cardiomyogenesis, since engraftment of cells was as short as two days.

Moreover, since 2011, several clinical trials have been carried out either to assess the safety and tolerability of a single dose of PDA001 (Phase I) or the safety and tolerability of PDA001 at 3 different dose levels plus its biologic effect once transplanted into humans (Phase II). The conditions evaluated included pulmonary sarcoidosis (NCT01440192), Crohn's disease (NCT01155362 and NCT01769755), rheumatoid arthritis (NCT01261403) and ischemic stroke (NCT01310114). Although good results are expected, the limited information available does not allow us to draw significant conclusions yet [132] [136]. We can only ascertain that, in some cases, it may cause mild to moderate side effects which most frequently include headache, pyrexia, and nausea.

MEDIPOST also developed a stem cell-based therapy consisting of a combination of human UC blood-derived MSCs (UCB-MSCs) and sodium hyaluronate which is already commercialized in Korea under the name of Cartistem® (NCT01041001). It was the world's first allogeneic stem cell drug launched into the market and is intended for the treatment of knee cartilage defects in patients with osteoarthritis caused by degeneration or repetitive trauma. Moreover, this technology is also being evaluated in clinical trials for the treatment of bronchopulmonary dysplasia and Alzheimer's disease, under the names of Pneumostem® (NCT04003857) and Neurostem® (NCT03172117) respectively. These treatments are based on the synthesis and local release of several paracrine factors by UCB-MSCs which serve as therapeutic agents to enhance or inhibit specific cell signalling pathways involved in the target disease. For example, Kim et al. demonstrated that UCB-MSCs have neuroprotective effects *in vitro* against amyloid-β neurotoxicity, the main cause of neurons loss in Alzheimer, via secretion of galectin-3 and promoted synaptic activity through production of growth differentiation factor-15 [137] [138]. In another study, they also demonstrated that these cells can attenuate hyperoxia-induced lung injury by modulating host inflammatory responses and oxidative stress [139]. Remarkably, the same group explored the feasibility of engineered UCB-MSCs as effective delivery vehicles for therapeutic genes in the allogenic treatment of glioma. In this work, they shown that the tumor-targeting properties of engineered MSCs are increased in irradiated tumors so the two strategies can be coupled to enhance the therapeutic potential of the treatment [140].

3.3. Amniotic epithelial stem cells (AECs)

AECs are another source of stem cells that can be readily harvested from perinatal tissues. As the name suggests, AECs can be found on the epithelium of the AM, where they are in direct contact with the amniotic fluid. Besides the typical advantageous features of stem cells, including self-renewal ability and the capacity to differentiate towards cells of the three

germ layers [141], AECs also possess characteristics commonly associated with MSCs (cell surface expression of CD90, CD105 and CD73, and lack of cell surface CD45, CD34, CD14, CD79 and HLA-DR) [142]. These features are evidenced in several works carried out by Miki et al. who have been largely dedicated to the study and characterization of these cells. To date, they successfully demonstrated that AECs express, although in an uniform manner, mRNA and proteins usually present in human embryonic stem cells (e.g. stage-specific embryonic antigen (SSEA)-3 and -4, nanog, octamer-binding transcription factor (Oct)-4 and T cell receptor alpha locus (TRA) 1-60 and 1-81) and rarely express HLA class IA and class II, therefore suggesting the potential clinical use of these cells [143]. Notably, they also proved that AECs are a safe (not form teratomas upon transplantation), readily available (can be easily harvest from AM using non-invasive procedures) [144] and almost limitless (with an average yield of more than 100 million AECs per discarded amnion) source of stem cells, that can be applied in cost-effective cellular therapies for the treatment of various conditions [145] [141].

Similarly, to AM grafts, also AECs have been widely investigated for their immune privilege [32]. Although no consensus has yet been reached on the mechanisms that mediate the low immunogenicity of AECs, it is thought to be related to low expression of cell surface HLA class I antigens, as well as to the expression of unique HLA class Ib molecules (e.g. HLA-G) that are known to supresses immune responses [145]. In addition to the low immunogenicity, AECs also exert immunomodulatory effects, under specific conditions, that may result from paracrine signalling events where multiple soluble factors are secreted to regulate immune responses [117]. Some of the molecules suspected to be involved on this mechanism are IL (-4, -6, -8, -10, -13 and -21), TGF-β, toll-like receptors (TLR)-4, Fas ligand, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and indoleamine 2,3-dioxygenase [146]. From a clinic point of view, these are evidences that AECs could potentially be used to overcome some of the limitation currently faced by TERM, notably as regards to the immune rejection of allogeneic cells [32] [117]., the limited number of cells and poor availability of compatible donors. Moreover, their capacity to differentiate into cells of the three germ layers further increases their regenerative potential, to cover neurological, pancreatic, hepatic and heart diseases [147]. It was in this scope, that several pre-clinical and clinical trials were performed in past years. Currently, at least 7 clinical trials are being prepared which intend to investigate the safety and effectiveness of human AECs for the treatment of Asherman's syndrome, primary ovarian insufficiency (infertility), non-union of limb fracture, bronchial fistula, chronic disease of the spinal cord, spastic cerebral palsy, and also for the prevention of acute-graft-versus-host disease after HSC transplantation. One

additional trial was registered on ANZCTR which intends to assess the safety of allogeneic AECs in ischemic stroke patients [148] In a previous work, the same group demonstrated that, after intravenous injection in animal models of stroke (including mices and non-human primates), AECs were able to migrate to the ischemic brain via chemotactic mechanisms and reduce brain inflammation, infarct development and functional deficits [149]. In addition, other studies also demonstrated that AECs can promote neuroprotection during the acute phase of neuronal injury and facilitate neuroregeneration in models of central nervous system disorders [150] [151]. These findings highly support that positive outcomes may result from this phase I clinical trial, possibly paving the way for the clinical application of AECs in neural therapies.

Interestingly, previous research on AECs has been highly focused on different applications, including liver regeneration. Transplantation of allogeneic hepatocytes is already considered a valuable alternative to whole-organ transplantation, however with the same limitation of liver availability. To overcome this cell shortage problem, stem cell therapies have been evaluated in preclinical trials. Cumulative evidences suggest that AECs hold great promise for the treatment of various liver diseases, as they yielded promising results after being transplanted into animal models of human metabolic liver diseases [152] [153]. Furthermore, several studies have demonstrated their ability to differentiate into cells that display hepatic characteristics using rapid and effective differentiation protocols [154]. For instance, Liu et al. have recently investigated the therapeutic efficiency of AEC-derived hepatocyte-like cells (HLCs) to treat mice with acute hepatic failure [155]. The successful differentiation of AECs into functional HLCs was demonstrated by the production of urea, secretion of alkaline phosphatase, uptake of indocyanine green, storage of glycogen, and expression of cytochromes P450 enzymes. HLCs were then transplanted into an animal model of liver injury to evaluate their therapeutic. Notably, not only the liver function was significantly improved, as there was also a significant increase in the survival rates of mice. Although the mechanisms behind these results have not been yet elucidated, the authors suggest three possible reasons: (1) the transplanted HLCs may fuse with hepatocytes and replacement of the damaged hepatocyte; (2) transplanted HLCs may support and activate liver stem cells or progenitor cells, which then further initiate endogenous cell proliferation and differentiation; or (3) transplanted HLCs may secrete multiple cytokines and growth factors that will inhibit inflammation and accelerate liver restoration. This description meets most of the explanations found in similar reports, where stem cells are used in TERM strategies. This may suggest that future work must be focused not only in prove the efficiency of cells in

specific conditions, but also (and most importantly) investigate the mechanisms behind this therapeutic effect, so that improved cell therapies can finally reach patients.

4. Conclusions and future perspectives

In the past few decades, TERM has evolved as a promising interdisciplinary field that combines cells, scaffolds and bioactive molecules to restore or regenerate damaged tissues. Although great advances have been done regarding the design of biocompatible scaffolds and their conjugation with stem cells, some issues continue to hamper the clinical translation of these therapies. The use of animal sources to prepare platforms for cell culture, for example, continues to raise ethical and safety concerns due to the frequency of immunogenic rejection and the risk of xenogeneic diseases transmission; on the other hand, the use of cadaveric and fetal human tissues is usually associated with serious ethical and/or legal concerns which highly limit their use. Alternatively, human perinatal tissues have recently started to be explored as a valuable source of materials and stem cells for TERM.

It is clear from the works herein reviewed that the range of applications for perinatal tissues-derived materials and cells has been exponentially growing. So far, researchers proved that these materials are capable of improve healing and promote regeneration mainly due to their anti-inflammatory, anti-fibrotic, immunomodulatory and anti-bacterial properties. Although these properties are intrinsically associated to perinatal tissues, it is now well established that resident stem cell populations also play a pivotal role on the bioactivity of these biomaterials by synthesizing and releasing factors involved in paracrine signalling. Therefore, not only perinatal tissues but also their derivate cells have been isolated and used to develop innovative therapies in current times.

Even though some of these tissues are already used to produce commercial products, such as the amniotic and chorionic membranes, the exploration of these materials is still at a very early stage. Evidence of that, is the fact that most of available products continue to be sell in the form of fresh, cryopreserved or dehydrated tissue sheets thus limiting their widespread application. A recent trend towards the development of injectable matrices and hydrogels may boost the commercial value of these tissues by increasing their relevance in TERM strategies, particularly as delivery vehicles for drugs, proteins and living cells. Despite the undeniable potential of such scaffolds, some limitations remain to be addressed, especially regarding their low stability and fast degradation rates. Hence, for these strategies to be successful it is imperative the development of appropriate protocols that improve the mechanical properties of perinatal tissue-derived scaffolds while retaining their original composition. This kind of formulation also offers the advantage of producing more versatile

scaffolds that can be combined to novel technologies, such as 3D printing and microfluidic chips.

In conclusion, a new era of natural animal-free solutions may emerge from the use of perinatal tissues. Adding to their human origin, other advantages result from their placental derivation which include good biocompatibility, readily availability, ethical-sourcing and cost effectiveness, thus meeting the criteria for the development of advanced TERM strategies. Moreover, increased safety and faster clinical outcomes are also major advantages that must be addressed. Therefore, coming years will certainly be of great innovation and development in the field of biomaterials and cell therapies, where perinatal derivates may play a pivotal role.

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