

Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik
Gynäkologie • Kontrazeption • Psychosomatik • Reproduktionsmedizin • Urologie



Human Placenta: a Source of Progenitor/Stem Cells?

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J. Reproduktionsmed. Endokrinol 2006; 3 (2), 117-126

www.kup.at/repromedizin

Online-Datenbank mit Autoren- und Stichwortsuche

Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, D-I-R, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz



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Human Placenta: a Source of Progenitor/Stem Cells?

O. Parolini, M. Soncini

Regenerative medicine based on cell therapy and tissue engineering methodologies is a newly emerging, multidisciplinary field involving biology, medicine, and genetic manipulation. This type of therapy is aimed at maintaining, restoring, or enhancing tissue and organ function, and is intended to assist in the treatment of a number of human conditions which range in severity from chronic to life threatening. In diseases where tissue or organ function is compromised, stem cell research holds great promise for providing an efficient avenue for regenerative therapy. However, the application of this type of research to the treatment of human disease will not be possible until much more is known about the biological properties of all types of stem cells. In the context of disease treatment, decisions will need to be made as to which is the best type of stem cell to use. Whether it is better to identify a stem cell able to differentiate into all tissue and organ types as opposed to using committed, lineage-specific stem cells, or perhaps embryonic cells are better than adult-derived stem cells, as well as the possible clinical applications of these cells. For some time, these questions have not only required significant scientific and medical consideration, but have also posed important social and ethical questions.

There is no doubt that stem cells hold great therapeutic potential, however there is still much research required before their use can be accepted as a valuable tool in disease treatment. In particular, it is necessary to identify a source of stem cells that is easily accessible, provides a high cell yield and for which cell recovery does not provoke serious ethical debate. The aim of this review is to consider and discuss the findings regarding a new source of "adult" stem cells isolated from human term placenta tissue. So far, the placental tissue has generally been discarded post partum, but it is now becoming recognised as a potential source of stem and progenitor cells. New findings now show that this tissue holds visible promise as a source of stem cells which may have widespread clinical applications, but which also circumvents the heated ethical debate which is associated commonly with the use of embryonically derived stem cells. Aspects including *in vitro* findings, pre-clinical experimentation, and immunological properties of stem cells isolated from placental membranes will be discussed in the context of their potential clinical applications. *J Reproduktionsmed Endokrinol* 2006; 3 (2): 117–26.

Key words: placenta, fetal membranes, amnion, chorion, stem cells, mesenchymal cells

Even though stem cells and their potential applications have emerged as a potential oasis in the field of disease treatment, there is a difference of opinion among scientists even in the definition of the term "stem cell", which at this point is still clearly an evolving concept [1]. Stem cells are generically defined as undifferentiated cells capable both of self-renewal through replication, as well as differentiation into specific cell lineages. Stem cell self-renewal may be perpetuated over many generations and can result in not only considerable amplification of stem cell numbers, but can also give rise to progeny that are more differentiated than the parent stem cells, known as progenitor or precursor cells. Importantly, these cells are capable only of further differentiation, but not self-renewal. By convention, cells are defined according to their ability to differentiate into other cell types: totipotent cells have the genetic potential to create every cell type of the body as well as placental and extra-embryonic tissues. Totipotent cells therefore have all of the properties necessary to form an entire human fetus, a property retained by the zygote up to 8 cell stage; pluripotent cells can be isolated from the inner cell mass of the blastocyst, meaning they each have the potential to create every cell of the body but not the necessary placenta and extra-embryonic tissues; multipotent cells can form a small number of cells/tissues that are usually restricted to a particular germ layer origin, and can be found in both developing fetuses and fully developed human beings; unipotent stem cells give rise to a single mature cell type.

According to the developmental stage from which they are obtained, stem cells are generally classified as being embryonic, fetal or adult. Embryonic stem cells have un-

limited self-renewing capacity and multilineage differentiation potential. However, the use of these cells raises several ethical concerns due to the fact that current methods used for their procurement require destruction of the embryonic body. Furthermore, their clinical application seems to be hindered by the high rate of tumor induction after transplantation. Stem cells derived from adult tissues are considered to be more limited in their potential, however, they are currently the more versatile cells in the clinical arena. Indeed, since the initial discovery of stem cells from bone marrow transplantation studies, the field of stem cell research has grown to a point where it is now believed to have more confidence in the basis for effective cell therapy and tissue engineering approaches in the future.

Another important consideration, which must not be underestimated in the field of stem cell-based regenerative medicine, is the possibility of immunological rejection of transplanted stem cells by the recipient, which is a fundamental issue central to the field of clinical transplantation.

In this complex scenario, stem cells isolated from human term placenta represent a field of investigation which is still in its infancy, but that holds great promises on several fronts. Specifically, their plasticity, immune characteristics, and the lack of ethical barriers to their procurement, make them ideal candidates for the basis of further research into disease treatment.

Placenta Tissues: General Aspects

Before considering whether placental tissue can provide a source of stem or progenitor cells for research and clinical applications, it is useful to take a detailed look at this tissue and its embryological origin. The human placenta is a fetomaternal entity that consists of a fetal component (the chorionic plate) and a maternal component (the deciduas). The two parts are held together by chorionic villi that connect the cytotrophoblastic shell of the chori-

Received: March 3, 2006; accepted: April 10, 2006

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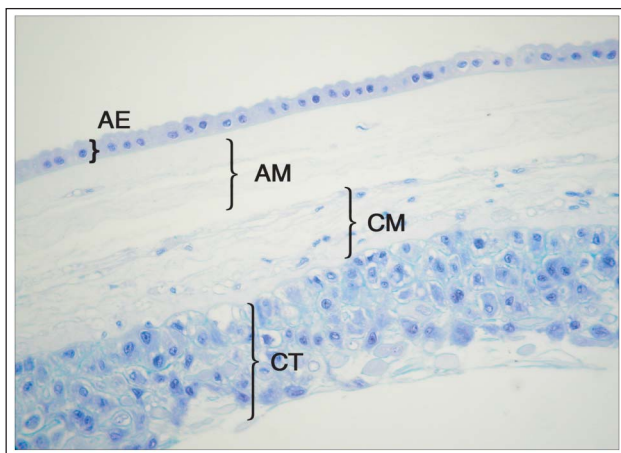


Figure 1. Morphology of fetal membranes of human term placenta (Giemsa staining; AE = amniotic epithelium layer; AM = amniotic mesenchymal layer; CM = chorionic mesenchymal layer; CT = chorionic trophoblastic layer)

onic sac to the deciduas basalis. The fetal part of the placenta, which includes the amniotic and chorionic fetal membranes, separates the fetus from the endometrium [2]. The amniochorionic membrane forms the outer limits of the sac that encloses the fetus and the innermost layer of this sac if formed by the amnion. The collagen-rich amnion confers tensile strength to the amniotic sac and results in the resistance to rupture typically observed in fetal membranes. As depicted in Figure 1, amnion and chorion are clearly distinguishable in the fetal component of the human term placenta.

Amnion is an unique avascular tissue and is comprised primarily of two cell types as also represented in Figure 1: the epithelial cuboid cells and the columnar cells. The amniotic epithelial cells (AE) on one side of the amnion create a continuous lining adjacent to the amniotic fluid, while on the other side of the amniotic epithelium is a thin layer of amniotic mesoderm (AM), throughout which a few fetal macrophages are sporadically distributed. The amniotic mesoderm is loosely connected to the chorionic mesoderm (CM), while the trophoblastic layer of the chorion (CT) which includes extravillous cytotrophoblast cells, represents the only residue of the former villi of the chorion frondosum.

The early origin of fetal membranes, which begin to develop even before gastrulation, gives rise to the possibility that cells in these membranes maintain the plasticity of pre-gastrulation embryo cells and therefore some degree of stemness that may allow their differentiation into different cell lineages. Figure 2 summarises the main steps in the development of embryonic and extraembryonic tissues as well as highlights the formation of the amnion and chorion.

At the blastocyst stage it is possible to distinguish the inner cell mass or embryoblast, which gives rise to the embryo and some extraembryonic tissues, as well as a blastocyst cavity and a thin outer layer of cells known as the trophoblast layer. This layer encloses the inner cell mass and the blastocyst cavity which later forms extraembryonic structures. As soon as the trophoblast layer attaches to the endometrial epithelium (5–6 days after

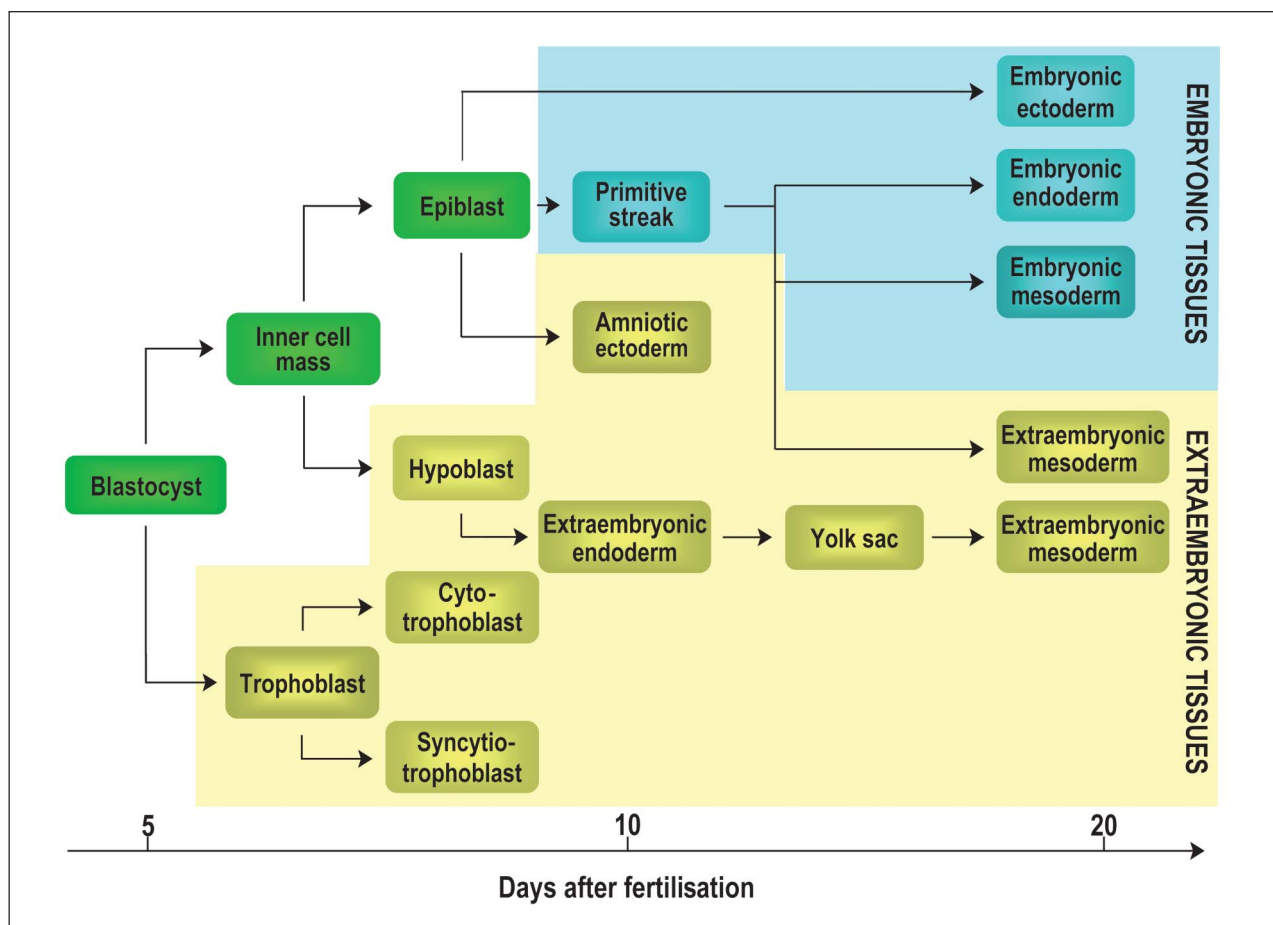


Figure 2. Schematic representation of embryonic and extraembryonic tissue development

fertilisation), the trophoblast starts to proliferate rapidly and differentiates into two layers: an outer layer of syncytiotrophoblast and an inner layer of cytotrophoblast. As implantation progresses into the second week from fertilisation, morphological changes occur in the inner cell mass giving rise to the bilaminar embryonic disc which is composed of two layers: the epiblast and the hypoblast. Meanwhile, the amniotic cavity appears in the inner cell mass, and together with the amnion forming cells, separates from the epiblast to form a thin membrane termed the amnion. The extraembryonic mesoderm, derived from the yolk sac, surrounds the amnion and lines the inner surface of the cytotrophoblast. The extraembryonic mesoderm and the two layers of the trophoblast constitute the chorion. Gastrulation is the next phase of embryonic development by which the embryo develops rapidly from the embryoblast and results in formation of a trilaminar embryonic disc. The three resultant germ layers – ectoderm, endoderm, and mesoderm – give rise to specific tissues and organs.

To briefly summarise, the amniotic epithelial region derives from the ectodermal epiblast, while the mesodermal regions of both the amnion (AM) and chorion (CM) derive from the extraembryonic mesoderm. As its name suggests, the trophoblastic region of chorion (CT) is derived from the trophoblast.

The amniotic membrane, which confers tensile strength to human fetal membranes that is associated with a high level of collagen synthesis [3], is the most widely studied region of the placenta tissue in terms of isolation of cells with potential clinical applications. Indeed, the amnion may not only protect the fetus from mechanical injury by containing it in the amniotic fluid, but it also synthesises and releases biologically active substances including cytokines and signaling molecules such as tumor necrosis factor, interferon, IL-4 [4], transforming growth factor- α [5], IL-6, IL-8 [6], and prostaglandins [5, 7, 8].

Interestingly, it has been shown that amniotic mesenchymal cells, but not epithelial cells, produce keratinocyte growth factor (KGF) [9]. KGF produced by the AM cells has been shown to increase AE cell growth *in vitro*, supporting the finding that KGF can act on epithelial cells to cause mitogenesis and differentiation [10]. KGF could therefore be important for mesenchymal-epithelial interactions, and may contribute to maintaining the function of this tissue.

What Can We Learn from the Early Studies and Original Use of Fetal Membranes?

Physicians and scientists have long recognised the potential for exploiting amnion and chorion tissue for therapeutic purposes. In 1910 Davis was the first to report the use of fetal membranes as surgical materials in skin transplantations [11]. Since then the applications of amniotic membranes in surgery have expanded to include treatment of skin wounds, burn injuries, chronic leg ulcers, and the prevention of tissue adhesion in surgical procedures [12–18]. More recently, remarkable therapeutic effects resulting from the use of amniotic membrane have been reported for ocular surface reconstruction where they are used for “substrate transplantation”, that is, the transplantation of basement membrane that promotes development of normal corneal or conjunctival epithelium

in patients with ocular surface disorders [19]. Recently, it has also been reported that human placental tissue provides a source of feeder cells for the growth of primate embryonic stem cells [20]. The exact nature of the support provided by the placenta tissue to these stem cells is not clear, however the known released growth factors (epidermal growth factor, basic fibroblast growth factor, transforming growth factor- α), and growth receptors (keratinocyte growth factor receptor and hepatocyte growth factor receptor) [21] are very likely able to contribute to the maintenance of undifferentiated embryonic stem cell cultures. It is also believed that amniotic membranes have antimicrobial properties [22] and antifibroblastic activity. While the exact mechanisms responsible for these properties have not yet been clearly defined, some hypotheses which have been proposed include down-regulation of transforming growth factor- β signalling [23, 24] and promotion of cell migration and growth [25]. It is very likely that different cell populations are required to drive these different functions. Recent studies have given some indication as to the exact fraction of the amniotic cells involved in wound healing: in an *in vitro* lesion repair assay, wound lesion repair capacities of amnion epithelial cells were compared to amnion mesenchymal cells. The results demonstrated that the lesion repair was complete in 40 hours in cultures containing amnion epithelial cells from both pre-term and term placenta, whereas repair was incomplete in cultures containing amnion mesenchymal cells [26].

Evidence of Presence of Stem/Progenitor Cells in the Placental Tissue

For the reasons presented above, the hypothesis can be proposed that cells present in the placental tissue, and in particular in the amniotic membrane, are capable of performing the main functions characteristic of stem cells: self-renewal, differentiation into multiple lineages, as well as the newly emerging notion that these cells create a microenvironment necessary for inducing local cell activation and proliferation. The last of these almost certainly plays a significant role in the wound lesion repair assay described above, by co-ordinating biological processes which include re-epithelialisation and reduction of inflammation. More recent studies, as reported in following sections, strongly indicate the presence of progenitor/stem cells with broad differentiation potential in various parts of the placenta.

As mentioned earlier, the placenta consists of three layers: amnion, chorion, and deciduas, each with different embryonic derivation, including ectodermal and mesodermal lineages. There have been reports suggesting that amniotic epithelial cells exhibit stem cell characteristics and may theoretically be useful in tissue-regeneration strategies.

Various approaches have been reported in order to isolate cells with stem and progenitor cell characteristics from placental tissues as summarised in a recent review [27]. Such cells have been isolated from the intact human term placenta [28], the fetal and the maternal portions of the placenta [29], the internal region of the placental lobules [30], the amniochorionic fetal membrane [31], the amniotic epithelium [32–44], and the amniotic mesenchyme [45, 46]. Mesenchymal cells have also been isolated from the human [47–49] and porcine amniotic

fluid [50]. However, it should be kept in mind that amniotic fluid is an environment with a very heterogeneous cell population, and besides the presence of cells derived from amnion, there are also cells belonging to skin, urogenital, respiratory, and digestive fetal systems.

Our own efforts have involved the characterisation of cells isolated from both the amniotic and chorionic fetal membranes. We have recently observed that human amnion and chorion cells from term placenta can engraft neonatal swine and rats following intra-peritoneal transplantation. Successful engraftment has been demonstrated by the observation of human micro-chimerism in various organs and tissues of animals sacrificed at different time points after cell transplantation, and by the detection of human-specific DNA sequences up to 120 days after cell inoculation. Interestingly, the ability of these cells to engraft different organs after IP transplantation indicates active migration characteristics as well as hom-

ing and long-term persistence within the local tissue environment. The preferred tissues for cell migration and engraftment appeared to be bone marrow, lungs, and thymus [31].

The following paragraphs describe in further detail some significant features of specific placenta-derived stem cells. The observations that these cells have multi-lineage differentiation potential, and can proliferate after attaching to scaffold structures, together with studies which suggest that they may be able to act as genetic carriers, has led researchers to initiate preclinical studies of cell therapy and tissue engineering using these cells. These studies are summarised in Table 1.

Amniotic Epithelial Cells (AEC)

As mentioned in previous paragraphs, the amnion and the three germ layers (endoderm, mesoderm, and ecto-

Table 1. Phenotype and differentiation potential of cells isolated from placental tissues and amniotic fluid

Cell types	<i>In vitro</i> studies	<i>In vivo</i> studies	Reference
Human amniotic and chorionic fetal membrane cells	• Expression of: – mesenchymal stem cell markers – adhesion molecules and integrins – pulmonary markers – transcription factors	• Engraftment after xenotransplantation in tissues of neonatal swine and rats and detection up to 120 days	[31]
Human amniotic epithelial cells	• Expression of neuronal and glial markers • Determination of active acetylcholine metabolism • Determination of synthesis and release of catecholamines • Expression of oligodendrocyte markers • Synthesis and release of neurotrophic factors • Overexpression of human β-glucuronidase by AEC after transduction • Synthesis of tyrosine hydroxylase and production of dopamine • Synthesis and release of activin and noggin • Expression of dopamine receptors • Promotion of survival of embryonic DA cells by conditioned medium from AEC • Expression of α-fetoprotein and albumin • Albumin production • Expression of – embryonic stem cell-related markers – pancreatic α- and β-cell markers • Expression of a subset of hepatocyte-related genes • Albumin and α-antitrypsin production • Expression of – embryonic stem cell markers – stem cell transcription factors • Differentiation into endoderm, mesoderm, ectoderm lineages • Expression of neuronal markers	• Partial correction of lysosomal storage disease in a mouse model of MPSVII after transplantation with transduced AEC that overexpress hGUSB • Engraftment and functionality of AEC after implantation into the striatum of a rat model of Parkinson's disease • Neuroprotective ability of AEC after implantation into midbrain of rats with 6-OHDA lesions • Transplanted into the spinal cord of bonnet monkeys survive, support the growth of host axons and prevent death of axotomised neurons • Integration into hepatic parenchyma after injection into the portal vein of SCID-mice • Differentiation into β-cells after transplantation into diabetic mice • Engraftment and albumin production after intra-peritoneal transplantation into SCID-mice • Not tumorigenic up to 7 months after transplantation • Engraftment and transformation into neuron-like cells after implantation into ischaemic brain of gerbils	[32] [33] [34] [35] [36] [37] [39] [40] [42–44] [52] [53] [55] [54] [56] [51] [57]

Continued on the next page

derm) of the embryo all originate from the epiblast. Recent studies aimed at defining the stem cell-like characteristics of amniotic cells show that AEC express some of the surface markers associated with embryonic stem cells. These include SSEA- (stage-specific embryonic-antigen-) 3, SSEA-4, TRA- (tumor rejection antigen) 1-60, and TRA-1-81. These cells also express pluripotent stem cell-specific transcription factors such as octamer binding protein 4 (OCT-4) and nanog. Additional experiments demonstrated *in vitro* differentiation of these cells into the three germ layers, in cardiac cells (mesodermal lineage), neuronal, and glial cells (ectodermal lineage), and pancreatic and hepatic differentiation (endodermal lineage) all show positivity for specific markers [51]. Neural differentiation of amniotic epithelial cells was also previously reported by Sakuragawa et al., who demonstrated that AEC express cellular markers of both neural and glial cells as well as those of oligodendrocytes [32, 35]. The AEC produce molecules involved in neuronal develop-

ment such as acetylcholine [33], catecholamines [34] including dopamine [39], and catecholamine receptors [42–44] and synthesise and release the brain-derived neurotrophic factor neurotrophin 3, nerve growth factor [36], activin, and noggin [40]. These findings support the hypothesis that human amnion might be involved in neural formation during early development [40], and raise the possibility that cells derived from this tissue could offer avenues for significant advancement in the treatment of neurodegenerative diseases. Indeed, the ability of human AEC to act as donor cells for allogeneic cell transplantation in a drug delivery system has been verified in an intracerebral grafting experiment for treatment in a rat model of Parkinson disease, showing that human AEC are capable of producing dopamine and can survive and function in the rat brain *in vivo* [39, 52]. In another model of neural disorder, rat amniotic epithelial cells were genetically engineered to express and secrete human beta-glucuronidase, and subsequently transplanted into a

Table 1 (continued). Phenotype and differentiation potential of cells isolated from placental tissues and amniotic fluid

Cell types	<i>In vitro</i> studies	<i>In vivo</i> studies	Reference
Rat amniotic epithelial cells		• Expression of exogenous genes after transplantation of transfected AEC into fetal rat liver up to 14 days after birth	[41]
Monkey amniotic epithelial cells	• Synthesis and release of catecholamines • Expression of dopamine receptors		[58, 59]
		• <i>In vitro</i> reconstitution of human and murine β -glucuronidase deficient cell lines by addition of conditioned media from mAEC overexpressing hGUSB	[38]
Human amniotic mesenchymal cells	• Expression of neuroglial markers		[45]
	• Expression of cardiac-specific genes and transcription factors • Differentiation into cardiomyocyte-like cells	• Engraftment and differentiation into cardiomyocyte-like cells after transplantation into rat myocardium	[46]
Human amniotic mesenchymal and epithelial cells	• 3-dimensional cultures for tissue engineering purposes		[26]
Human mesenchymal progenitor cells from trophoblast	• Mesenchymal stem cell phenotype • Expression of embryonic stem cell markers • Differentiation into adipo-, chondro-, osteogenic like cells • Differentiation into neurogenic cells • Differentiation into myogenic cells • Determination of expression of genes associated with the mesoderm, ectoderm and endoderm lineages		[28, 30, 60, 61, 62, 63]
	• Mesenchymal stem cell phenotype • Differentiation into chondrogenic cells in atelocollagen gel	• Chondrogenic differentiation after transplantation into nude rats with osteochondral defect	[64]
Human mesenchymal cells from maternal and fetal placental regions	• Mesenchymal stem cell phenotype • Differentiation into adipo-, osteogenic cells		[29]
Human amniotic and chorionic mesenchymal cells	• Mesenchymal stem cell-like phenotype • Differentiation into osteo-, adipo-, chondrogenic cells		Soncini M et al. (in prep.)
Mesenchymal cells from human amniotic fluid	• Mesenchymal stem cell phenotype		[48]
	• Expression of OCT-4, vimentin, ALP		[47]
	• Mesenchymal stem cell phenotype • Presence of a subpopulation of OCT-4 positive cells • Differentiation into adipo-, osteogenic and neurogenic cells • Expression of neuronal markers		[49, 65]
Mesenchymal cells from porcine amniotic fluid	• Expression of mesenchymal and stem cell markers		[50]

AEC = amniotic epithelial cells; GUSB = human β -glucuronidase; OCT-4 = octamer binding protein 4; SCID = severe combined immunodeficiency; 6-OHDA = 6-hydroxydopamine

mouse model of mucopolysaccharidosis type VII, resulting in an improvement of the lysosomal storage disorder [37, 38].

Although they show very promising results, these studies are still in their infancy and the functional correction of the regenerated tissues and organs requires further investigation.

More recently, Sankar and collaborators have investigated the potential of AEC to assist in the treatment of spinal cord injury. Human AEC were transplanted into transection cavities in the spinal cords of bonnet monkeys, and were able to survive for at least 60 days. Furthermore, there were no signs of glial scarring at the cut ends, serving as a likely indication that the transplanted cells were able to act as a suitable milieu for the host axons to grow, and that they may also have prevented death in axotomised cells or stimulated growth of collateral sprouting. Although very preliminary, the authors raise the speculation that human AEC may have similar beneficial effects if transplanted to repair spinal cord injuries [53].

Although there has been much knowledge gained from the studies just discussed, there is still much more investigation which must be carried out in order to validate a role for amniotic epithelial cells in neuronal development and their prospective use for treatment of neuronal diseases. Interestingly, as mentioned in a previous study [51], the applications of AEC seem to be broader than those already discussed. It has been reported that human AEC can differentiate *in vitro* into insulin-producing cells. In addition, *in vivo* studies have demonstrated that human AEC are capable of normalising blood glucose levels for several months after transplantation into the spleens of diabetic SCID- (severe combined immunodeficiency-) mice [54]. These results suggest that human AEC have the potential to differentiate into β -cells *in vivo* and therefore may have therapeutic potential for the treatment of type I diabetes mellitus. Furthermore, human AEC shown to synthesise and excrete albumin *in vitro*, when genetically modified to express the LacZ gene for tracking purposes and subsequently transplanted through the portal vein of the SCID-mice, were shown to migrate into the liver parenchyma within a few days of injection, where they showed positive immunoreactivity for human albumin and alpha-fetoprotein [55]. This suggests a potential role for these cells in liver tissue regeneration. In addition, these experiments provide indirect evidence supporting the possibility of using AEC as a gene delivery tool, as also suggested in other studies [37, 38, 41]. The same group led by Sakuragawa reported that *in utero* transplantation of genetically engineered AEC into fetal rat liver [41] resulted in expression of exogenous transfected genes for up to 14 days after birth, a longer time than observed for transfected hepatocytes or direct viral vector injection.

Mesenchymal Stem Cells in the Placenta

Recently, there has been growing interest in mesenchymal stem cells because they are thought to be multipotent. Indeed, there are many reports showing that bone marrow-derived mesenchymal stem cells (MSC) are able to differentiate into all the mesodermic lineages: adipose and connective tissue, as well as bone and cartilage [66]. Interestingly, the Verfaillie group has shown the existence

of stem cells defined as multipotent adult progenitor cells (MAPCs) in the bone marrow. MAPCs are able to differentiate not only into mesenchymal cells but also into ectoderm and neuroectoderm lineages [67].

MSC were initially identified in human post-natal bone marrow and subsequently isolated from other tissues such as adipose tissue, peripheral blood, cord blood, and adult connective tissue [68–70]. It is recognised that these MSC have the capacity to contribute to the regeneration of mesenchymal tissues and to support expansion of haematopoietic stem cells as shown by *in vitro* reconstruction experiments of the haematopoietic microenvironment [71, 72]. Furthermore, several studies have revealed that MSC are not immunogenic and also exhibit immunoregulatory properties [73]. The mechanisms responsible for these observations have not yet been clarified, however *in vitro* experiments have demonstrated that MSC can induce down-regulation of T cell proliferation [74] and inhibition of differentiation and proliferation of monocytes [75]. Therefore, the potential clinical applications of MSC are becoming more and more significant [76] and can be envisioned to further improve the haematopoietic cell engraftment rates and amelioration as well as prevention of graft vs. host reactions. Currently bone marrow represents the main source of MSC for both experimental and clinical studies. However, there are limitations to the use of this tissue: bone marrow harvest is an invasive procedure; there are clear limitations to the availability and frequency of MSC from bone marrow; stem cell differentiation capacity is known to decrease with the age of the donor [77]; and furthermore there is an increasing number of possible viral infections that the donor may carry. Therefore the search for other sources of mesenchymal cells is clearly an important priority for stem cell research. To this end, different fetal tissues including first trimester fetal bone marrow, blood, liver, spleen, and kidney have been investigated [78, 79]. These, however, do not represent easily available sources. Several groups, including ours, are therefore focussing their attention on the isolation and study of mesenchymal cells from human term placenta, and are also attempting preclinical studies in different animal models [31]. So far there is not any specific cellular marker for definition and isolation of MSC, and even though the list of indirect markers is growing, the phenotypic determination of MSC identity is so far based on expression of SH2/CD105, CD29, CD44, CD73/SH3, CD166 (ALCAM), and CD90/THY1, in the absence of haematopoietic markers CD34, CD45, and Glycophorin A [66]. Most commonly, MSC isolation is performed by simple plastic adhesion of total bone marrow cells [80].

Different groups have reported the isolation of mesenchymal stem cell-like cells from different areas of the placenta, and the data so far available are reported in Table 1. Some groups have focused their attention on the placental tissue either before or after removal of the fetal membranes [30, 60, 61] from maternal and fetal sides of the placenta [29], while others have considered both the amniotic and chorionic fetal membranes [31], the amniotic mesenchymal region [45, 46] and also human amniotic fluid [47–49, 65].

Interestingly, a population of multipotent cells, which have been termed placenta-derived multipotent cells (PDMCs), has been described by Yen and collaborators [28]. These cells not only present with a mesenchymal

phenotype, but they are also positive for the embryonic stem cell markers SSEA-4, TRA-1-61, TRA-1-80, and OCT-4, while they lack endothelial and trophoblastic markers. Besides the phenotypical analysis, the differentiation potential of these cells has also been reported (Tab. 1). Differentiation of placental MSC toward mature mesenchymal cell types including osteo-, chondro-, and adipogenic lineages has been reported by various authors [30, 60, 61, 62–64]. However, more readout systems have to be employed in order to prove the true differentiation potential of these cells. On the other hand, PDMCs which have been described with a more undifferentiated phenotype displayed the ability to differentiate into mesodermal lineage cells as well as ectodermal neuron-like cells [28]. *In vitro* neuroglial differentiation has also been shown for amnion derived mesenchymal cells, as reported by Sakuragawa and collaborators [45].

Zhao and collaborators [46] demonstrated that amniotic mesenchymal cells, but not the amniotic epithelial cells, can differentiate into cardiomyocyte-like cells after culture with factors which induce cardiomyogenic differentiation, and also after co-culture experiments with neonatal rat heart explants. Xenotransplantation into the myocardial infarct of rats demonstrated that human amniotic mesenchymal cells could undergo myocardial differentiation and were able to survive as long as 2 months at the scar side. Even though it will be necessary to demonstrate functional regeneration to support the application of amniotic mesenchymal cells in myocardial infarction, these preliminary data further support the engraftment capability of these cells and highlight their potential for clinical applications.

Taken together, the findings described above are consistent with the possibility that placenta tissue can act as a source of not only mesenchymal progenitor cells, but also of multipotent cells, although it remains to be demonstrated that multi-lineage differentiation observation comes from a clonal population.

Immunological Characteristics of Human Fetal Membranes

More than fifty years after the paradox of maternal tolerance was first raised by Peter Medawar, the mechanisms of protection of the allogeneic fetus from the maternal immune response during pregnancy still remain mysterious.

Excellent reviews on the immunobiology of pregnancy are available, which address issues such as trophoblast cell biology and anatomy, the role of fetal antigen presentation, uterine macrophages and NK cells, cytokine production, immunoregulation, tolerance and the innate immune system during pregnancy [81–85]. Here we intend to discuss the hypothesis that in the maternal-fetal interface cells present in the fetal membrane may play a role in immunoregulation. Indeed, the absence of rejection of the amniotic membranes which have been used in past clinical applications for treatment of burn injury and skin ulcers [13, 16], and more recently for applications in ophthalmology [19], is associated with an emerging general consensus regarding the reduced immunogenicity of amniotic epithelial cells, explained by the notion that these cells are thought to express no class II antigens, and very reduced levels of the class Ib antigens HLA-E and

HLA-G [86]. The HLA-G molecule displays at least four inhibitory functions relevant to immune responses: first, it can bind directly to inhibitory receptors found on NK cells and other leukocytes [87, 88]; secondly, it possesses the appropriate leader peptide for binding to HLA-E, which will in turn inhibit NK cells via their CD94/NKG2 receptors [89]; thirdly, as shown recently, soluble forms of HLA-G produced by placental cells induce apoptosis of activated CD8+ T cells [90]; finally HLA-G can inhibit CD4+ T cell proliferation [91].

In vitro experiments using supernatants from short term cultures of human placenta have demonstrated inhibition of PHA- (phytohaemagglutinin-) driven lymphocyte activation, mixed lymphocyte reaction and natural killer activity [92, 93]. Additional experiments have shown that fragments of amniotic membrane exert immunosuppressive properties in mixed lymphocyte reactions [94].

Li et al. have cultured mononuclear cells derived from placenta in mesenchymal stem cell medium, in order to favour the growth and expansion of this cell population. These cells were then shown to suppress umbilical cord blood (UCB) lymphocyte proliferation which had been induced by cellular or non-specific mitogenic stimuli [95].

We have recently demonstrated that cells isolated from amniotic and chorionic fetal membranes do not induce an allo-, or a xenogeneic immune response. These cells also have the capacity to suppress alloreactive T cells in a mixed lymphocyte reaction. Furthermore, these cells were able to suppress allogeneic human MLR even when direct cell contact was prevented by a transwell membrane, suggesting active secretion of soluble inhibitors [31]. All of these characteristics make fetal membrane cells particularly interesting in the context of cell therapy applications, as lack of immunogenicity is a very important feature in situations involving allo-transplantation.

Furthermore, a recent study has demonstrated that human placenta mesenchymal progenitor cells support *in vitro* expansion of CD34+ haematopoietic stem cells [60]. This feature, together with the lack of immunogenicity and the immunomodulatory characteristics of mesenchymal cells, suggests that the combined harvesting of mesenchymal cells from placenta, and haematopoietic stem cells from umbilical cord blood, could result in an important approach for cotransplantation that would not augment haematopoietic stem cell engraftment, but could even hold the potential to be used to aid in reduction of potential graft versus host disease (GVHD) in recipients.

Conclusions: Where Do We Stand and What Are the Open Questions?

The findings presented above indicate that cells isolated from the placenta possess interesting characteristics. These cells have the potential to differentiate into a variety of cell lineages, which together with their reduced immunogenicity, it makes them very attractive for potential clinical cell therapy and tissue engineering approaches. Other studies discussed suggest that the application of these cells could even extend toward use as carriers in gene therapy based approaches. These cells can be cryopreserved and show long term survival, and unlike embryonic stem cells so far display no evidence of

forming neoplasm after transplantation, therefore further supporting their potential value in clinical therapy applications. Moreover, since the placental tissue is normally discarded post partum, its use raises no ethical controversy, and its procurement is safe, non-invasive, and non-restricted in availability.

In the complex field of stem cells, the potential use of this alternative cell source is subordinate to many open questions that require further extensive studies. These will include purification of progenitor cell subtypes to better define the potential for differentiation into specific lineages, determination of their long-term self renewal potential, and demonstration of true multipotential differentiation by subsequent clonal analysis. In addition, although to date no uncontrolled proliferation of these cells has been reported after transplantation, safety studies must be performed at least for the cells deriving from cytotrophoblast because of their known invasiveness potential. Finally, the definition of the soluble factors associated with the immunoregulatory capabilities of these cells, the identification of the cell population(s) responsible for the production of these factors, and elucidation of the mechanisms underlying such phenomena, will provide additional crucial information. In conclusion, while the title of Dr. Heeger's editorial: "Amnion and Chorion Cells as Therapeutic Agents for Transplantation and Tissue Regeneration: A Field in Its Infancy" [96] captures the current status and the challenges of the field, the ongoing lines of research will generate the necessary knowledge of the properties of cells isolated from fetal membranes that will translate in their application to a variety of clinical settings.

Acknowledgments

This work was in parts funded by Fondazione Cariplo, Istituto Superiore di Sanità, Ministero dell'Università e della Ricerca, Ministero della Salute, Italy.

We wish to thank Dr. Fabio Candotti for critical reading of the article and Marco Evangelista for editorial assistance.

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