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SHORT ARTICLE

Human term placenta as source of stem cells for regenerative medicine

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Abstract

A goal of regenerative medicine is to repair and regenerate damaged cells, tissues, and organs and ultimately restore function. Regeneration can be obtained by cell replacement or by stimulating the body's own repair mechanisms. It requires a favorable microenvironment so that regenerative signals can stimulate resident stem/stromal cells. Regeneration is only possible after resolution of injury-induced inflammation. Immune response may be aggravated in degenerative, inflammation-based diseases.

In this mini-review we discuss how cells isolated from the amniotic membrane of human term placentas and their derivatives, such as conditioned cell culture medium, can help resolve many diseases characterized by altered immune response by acting on different inflammatory mediators.

Amniotic cells and derivatives have a wide spectrum of immunomodulatory properties that help trigger tissue regeneration. They can promote resolution of injury-related inflammation by reducing pro-inflammatory signals and favoring anti-inflammatory immune components.

The multifaceted, immunomodulatory properties of amniotic membrane-derived cells and derivatives make them attractive for a variety of applications, especially in diseases with an exacerbated immune response, such as degenerative, inflammatory-based diseases.

Keywords: regenerative medicine, immunomodulation, paracrine, human term placenta, amniotic membrane, mesenchymal stromal/stem cells

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Introduction

The modern view of regenerative medicine is concerned more with the immunomodulatory potential of mesenchymal stromal/stem cells (MSC) as a key to regeneration, than with their differentiation capacity. Mesenchymal stromal/stem cells can be isolated from a variety of tissues. For over a decade, the human term placenta, long regarded as biological waste, has been the major source of MSC for several reasons, including lack of ethical concerns and ease of cell isolation. Moreover, placental MSC virtually lack expression of human leukocyte antigens and co-stimulatory molecules, making them very attractive for transplantation in allogeneic settings.

Human term placenta: a precious reservoir of cells

The human placenta plays the fundamental role of exchanging oxygen, nutrients and waste products between the mother and the growing fetus. It also maintains fetomaternal tolerance during pregnancy. The placenta is an oval or roundish organ of maternal and fetal origin that may vary in diameter (15–20 cm) and thickness (2-3 cm). The maternal side of the placenta is composed of the decidua, derived from the maternal endometrium (1). The fetal component includes all the placental tissues that originate from the blastocyst, including the placental disc, the amniotic and chorionic membranes (often referred to as fetal membranes), and the umbilical cord.[1] Starting from the fetus, the innermost part

of the placenta, that encloses the fetus in the amniotic sac and is in direct contact with amniotic fluid, is called the amniotic membrane (or amnion). The amnion is a thin, avascular sheet with epithelial and stromal layers. The amniotic epithelium is composed of a single layer of flat, cuboidal or columnar epithelial cells, uniformly arranged on a basement membrane (2). The amniotic epithelium also covers the umbilical cord, which is composed of the umbilical vein and two umbilical arteries embedded in a gelatinous proteoglycan-rich matrix, known as Wharton's jelly. The amniotic stroma is a compact collagen-rich acellular layer with widely dispersed fibroblast-like cells and rare macrophages. The chorion, or outermost membrane of the sac enclosing the fetus, comprises the chorionic stromal and trophoblastic layers (3).

A variety of cells with stem/progenitor properties have been isolated from the four major regions of the human term placenta, namely, amniotic epithelial, amniotic mesenchymal stromal, chorionic mesenchymal stromal and chorionic trophoblastic tissues. According to the First International Workshop on Placenta-Derived Stem Cells (4), the stem/progenitor cells that can be isolated from these regions are human amniotic epithelial cells (hAEC), human amniotic mesenchymal stromal cells (hAMSC), human chorionic mesenchymal stromal cells (hCMSC), and human chorionic trophoblastic cells (hCTC), respectively (4). Cells with characteristics of mesenchymal stromal/stem cells (MSC) can also be isolated from other placental regions, such as chorionic villi (5-8), decidua (9), and the umbilical cord (10, 12). The human placenta also harbors a wide variety of hematopoietic cells, as well as mature and immature hematopoietic progenitors and hematopoietic stem cells (13, 14).

Here we discuss how cells isolated from the amniotic membrane of human term placentas and their derivatives, such as conditioned cell culture medium, can help resolve many diseases characterized by altered immune response by acting on different inflammatory mediators.

The contribution of amniotic cells and their derivatives to tissue regeneration: immunomodulation

There is widespread interest in understanding how mesenchymal stem/stromal cells isolated from different tissues, including the placenta, can contribute to the regeneration of damaged tissues. On one hand, a more "traditional" widely-discussed mechanism is that of cell differentiation, whereby transplanted cells differentiate into tissue-specific cell types in order to replace damaged tissue (15, 16). On the other hand, a more modern and widely-accepted mechanism is that stem/stromal cells can act via paracrine signaling through release of bioactive mediators, which may stimulate resident target cells to proliferate or induce resident progenitor cells to differentiate.

Many groups have demonstrated that the bioactive mediators secreted by amniotic cells have immunomodulatory properties. Thus, a more contemporary proposed mechanism is that amniotic cells favor suppression of persistent exacerbated inflammation activated by injury, thus facilitating the repair and regeneration of damaged tissues.

We and others have demonstrated that amniotic cell transplant favors tissue repair and regeneration in rodent models of inflammation-based diseases, such as liver fibrosis (17,18), lung fibrosis (19-24). collagen-induced arthritis (25), inflammatory bowel disease (25), severe dextran-induced colitis (26), experimental autoimmune encephalomyelitis (EAE, an animal model for multiple sclerosis) (25), traumatic brain injury (27, 28), and cardiac ischemia (29-31).

Others have shown beneficial effects after transplant of amniotic cells in fetal models of lung injury, such as bronchopulmonary dysplasia-like injury induced by exposure to hyperoxic conditions (32), or ventilation-induced fetal lung injury (33), and also inflammation-induced fetal lung injury generated by intra-amniotic lipopolysaccharide (LPS) injection (34), Tissue regeneration has been shown to be induced by ovine amniotic epithelial cells (AEC) allotransplanted into sheep with experimentally-induced tendon lesions (35, 36).

It is progressively being demonstrated that paracrine mechanisms are largely responsible for the beneficial properties exerted by amniotic cells. In cases where amniotic cells were absent in injured tissues after transplantation, they are thought to produce factors that acted on nearby resident cells, improving their survival, proliferation, differentiation and function. Our group recently demonstrated that although human amniotic mesenchymal stromal cells (hAMSC) were absent in the brain after systemic injection, their administration to mice with traumatic brain injury increased neuronal rescue and vascular density in the injured cortex (27), In line with this, other groups have shown that in an ischemic stroke model, besides modulating peripheral and local inflammation, hAMSC produce factors with anti-apoptotic, neurogenic and angiogenic effects (37). Epithelial cells of the amniotic membrane (hAEC) have also been shown to promote cutaneous wound healing by enhancing the proliferation and migration of keratinocytes (38, 39).

In favor of the paracrine/secretory action of amniotic cells, several groups have demonstrated that the beneficial effects were also achieved with cell-free treatments, such as with conditioned media containing factors secreted by amniotic cells during culture *in vitro*. In fact, we and others have shown that conditioned medium from amniotic mesenchymal cell culture (CM-hAMSC) has beneficial effects in preclinical models of lung fibrosis (40, 41) and cardiac ischemia (42). More recently, our group demonstrated that CM-hAMSC accelerates the healing of ulcers in diabetic mice (43). Application of CM-hAMSC to spontaneous tendon and ligament injuries in horses has also been shown to significantly decrease the rate of subsequent injuries compared to untreated animals (44.) Other groups have reported therapeutic effects using conditioned medium containing factors secreted from amniotic epithelial cells (CM-hAEC) in corneal alkali injuries in rabbits (45) or in dogs with induced corneal ulcers (46). To further substantiate a paracrine mechanism of action, our group showed that release of soluble factors by amniotic cells is associated with

the therapeutic effects observed after treatment with amniotic membrane patches in models of liver fibrosis (47, 48) and cardiac ischemia (49).

In line with preclinical results, our *in vitro* studies sustain the immunomodulatory potential of amniotic cells. We showed that hAMSC reduce T cell proliferation induced by different stimuli (50) inhibit maturation of monocytes to dendritic cells (51) and induce macrophage differentiation into alternatively activated M2 macrophages (51). Our more recent results strongly support the notion ascribing the immunomodulatory properties of hAMSC to their secretome, as reported by studies using hAMSC in transwell systems (that prevent cell-to-cell contact), and those using their conditioned medium (CM-hAMSC). Specifically, hAMSC in transwells, and also their conditioned medium, induce anti-proliferative effects in T cells (50-53), skew T cell polarization, enhancing T regulatory cells and reducing Th1 and Th17 populations (54), and inhibit differentiation of monocyte-derived dendritic cells (51). Interestingly, we recently demonstrated that CM-hAMSC favors the M1 to M2-macrophage switch as well as enhancing M2 features, and that macrophages generated in the presence of CM-hAMSC enhance wound healing in diabetic mice (43).

Conclusions

Tissue injury triggers several overlapping events that lead to an inflammatory response. The latter involves recruitment of immune cells to the site of injury, under the control of molecular regulators. Inflammation plays a fundamental role in the regeneration of injured tissues. Acute self-limiting and self-resolving inflammation is a fundamental step for repair, whereas unresolved chronic inflammation can lead to tissue damage and deregulated tissue healing, ultimately causing a series of pathologies, including fibrosis and autoimmune diseases. Amniotic cells and derivatives act on different inflammatory mediators, participating in a resolution-promoting inflammatory response, and this seems to be the mechanism underlying their therapeutic effect, observed in different preclinical models.

Conflicts of interest

The authors declare that they have no competing interests or conflicts of interest in relation to this paper.

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