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Review Article

The relationship between amniotic epithelial cells and their microenvironment

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Abbreviations:
hAFC, human amniotic fluid cells
BM, basement membrane
ECM, extracellular matrix
hAEC, human amnion epithelial cells
hESC, human embryonic stem cells
hAM-MSC, human amnion mesenchymal stromal cells
IDO, indoleamine 2,3-dioxygenase

ABSTRACT

Human amniotic epithelial cells (hAEC) are characterized by a great ability to differentiate, and immunomodulatory properties toward mother's immune system cells. These features have been described as being able to change during pregnancy. Thanks to their unique properties: low immunogenicity and high effectiveness of transplantations, amniotic epithelial cells constitute a very attractive source of stem cells for practical purposes in regenerative medicine and transplantology. In this review, we focus on natural factors potentially determining hAEC immunophenotype during pregnancy. Recognition of the impact of specific factors on hAEC would help in effective isolation, creation of appropriate culture conditions and regulation of desired cell function. We also indicate immunomodulatory properties of hAEC themselves. Discovering relations of hAEC with the microenvironment seems to be crucial for their clinical application.

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LN, laminins
MSC, mesenchymal stem cells
PG, prostaglandins

Introduction

Perinatal tissues such as the placenta, play a special role as a source of stem cells due to the fact that, by nature, they are a reservoir of cells of fetal origin (Parolini et al., 2008). Human amnion preserves a significant number of cells with the characteristics of human embryonic stem cells (hESC) and similar potential to differentiation. Depending on structural layer and gestational age it is more or less efficient source of pluripotent and mesenchymal stem cells. Subpopulations of the cells expressing pluripotency markers, such as transcription factors (*i.e.* Sox-2, Nanog and Tert) or surface markers (*i.e.* TRA-1-60, TRA-1-81, SSEA-3 and SSEA-4), are significantly more numerous in early amnia as compared to term ones (Izumi et al., 2009). Among the advantages of amnion derived cells, a limited expression of the MHC antigens class I, as well as lack of MHC class II should be underlined. These properties are basic for a natural immunosuppression mechanism against the maternal defense system. Furthermore, they may be important for the safe amniotic cells therapeutic transplantation to enhance a process of tissue regeneration (Toda et al., 2007) or in a treatment of such diseases as stroke, liver disease or lung fibrosis (Manuelpillai et al., 2011). Additionally, human amniotic cells have anti-inflammatory (Silini et al., 2013) and low tumorigenic properties (Miki et al., 2005).

Human amnion derived cells are phenotypically heterogeneous. Two main populations are, as follows: human amniotic epithelial cells (hAEC) and human amnion mesenchymal stromal cells (hAM-MSC). Control of the regulation of gene expressions in these cells by environmental factors seems to be particularly important to maintain their own properties as low-differentiated cells. hAEC are placed in the niche which is located between two different microenvironments: amniotic fluid and basement membrane (BM). It means that hAEC are exposed, on one hand – to the influence of amniotic fluid soluble components, on the other hand – to the insoluble compounds of BM, *e.g.* collagens, fibronectin, nidogen, and laminins (Niknejad et al., 2012; Lambshead et al., 2013). These components are able to modify the phenotype of amniotic stem cells. Many of these effects, for example, increasing or decreasing proliferation and stemness of pluripotent cells, as well as their ability to differentiation, result from ligands interaction with integrin receptors (Domogatskaya et al., 2008; Rodin et al., 2010).

In addition, hAM-MSC are cells important as a source of numerous extracellular matrix (ECM) components which can influence the hAEC phenotype. These cells are located in the mesenchymal tissue underlying the epithelial BM. Finally, hAEC themselves, are potentially a prominent source of ECM components. The result of the action of the cellular and extracellular factors is a set of unique features, specific to amniotic cells, such as immunomodulating properties against mother's immune cells (Insausti et al., 2014; Yamahara et al., 2014). Expression of hAEC genes might be also a part of autoregulatory mechanism maintaining amniotic stem cells stemness or regulating differentiation.

Identification of microenvironmental components, which can affect amniotic stem cells and potentially play a key role in the fate of these cells, seems to be crucial for the *in vitro* reconstitution of the natural amniotic microenvironment, as well as modulation of the stem cell phenotype. A control of cell-to-cell and cell-to-ECM relationships dependent on amniotic fluid/BM/ECM components might be crucial for the management of stem cell immunophenotype both, in culture and clinical applications *in vivo*.

Development of human amnion epithelial cells' niche

Amnion development begins early, at the stage of gastrulation. At this stage, pluripotent epiblast cells start to form three primary germ layers of the embryo, as well as other extraembryonic tissues, including yolk sac and extraembryonic mesenchyme. From the very beginning of placenta development, hAEC are influenced by three main streams of stimuli (Fig. 1). The first comes from amniotic fluid surrounding the fetus, the second – from BM, the third – from underlying mesenchymal layer of the amnion (Murphy and Atala, 2013).

Amniotic fluid provides soluble factors to hAEC. These factors can support hAEC potency and immunomodulatory properties preventing both inflammation and fetus rejection. Amniotic fluid changes its content during gestation. At the

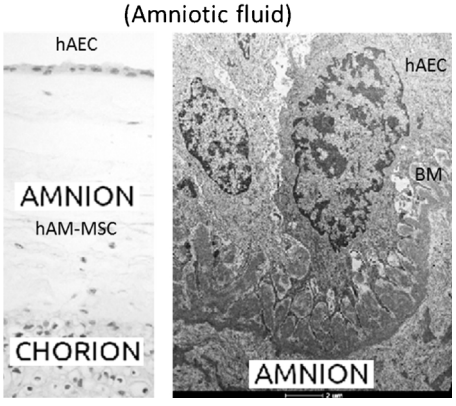

Fig. 1 – Topography of human amnion in H–E staining (left) and transmission electron microscopy (right). hAEC, human amnion epithelial cells; BM, basement membrane; hAM-MSC, human amnion mesenchymal stromal cells (Dept. of Cytophysiology, MUS).