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A Concise Review -Versatility of Amniotic Epithelial Stem Cells (hAECs)

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Abstract
Amniotic epithelial cells are generated from amnioblasts on the eighth day after fertilization and constitute the inner layer of the amnion. Many studies have demonstrated the differentiation potential of human amniotic epithelial cells (HAEC) into cells of all three germ layers. Its easy accessibly without any ethical constrains has made it an ideal non-controversial source of primary cells that can be differentiated in a plethora of organ specific lineages. The aim of this review is to highlight the versatility of hAECs whilst exploring its tri-lineage differentiation potential. Which makes these cells an ideal candidate for disease modeling and cellular replacement therapy.
Keywords: *Amniotic epithelial cells, cellular replacement therapy, disease modeling.*

Introduction

Human amniotic membrane is a rich source of stem cells. Isolated amniotic epithelial cells (hAECs) have especial properties that make them truly unique in comparison to other stem cell populations. Its ability to differentiate towards all three-germ layers make hAECspluripotent similar to embryonic stem cells (ESC) without the ethical constrains since placenta are discarded following delivery. In addition hAECs are non-tumorigenic and have immunosuppressive properties[1-3]. Due to these favorable characteristics of hAECs they have a variety of applications in cellular replacement therapies in diseases such as diabetes, neurodegenerative disorders, ischemic diseases (myocardial and brain infarct), spinal cord injury, etc. They can also be employed as a platform for drug and toxicology screening[4-6]. Through this literature review I wish to highlight the differentiation potential of hAECs along with their applications in modern medicine.

Practical advantages and differentiation potential of hAECs

Amniotic epithelial stem cells can be isolated with ease form the amniotic membrane following a 4-quadrant blunt dissection method. Followed by stripping off the amniotic membrane from the chorion and digested with trypsin or other digestive enzymes[7-9]. Epithelial cells are usually released following a brief digestive period of 20-30 minutes. These cells have a plastic adherence capacity and proliferate robustly in a simple complete media (Dulbecco's modified Eagle's medium supplemented with 5%–10% serum and L- Glutamine). They can be subcultured up to 5-6 passages before proliferation ceasesand display typical cuboidal epithelial morphology[10,11]. They express a variety of cell surface antigens includingATP-binding cassette transporter G2 (ABCG2/BCRP), CD9, CD24, E-cadherin, integrins α6 and β1, c-met (hepatocyte growth factor receptor), stage-specific embryonic antigens

(SSEAs) 3 and 4, and tumor rejection antigens 1-60 and 1-81, their overall low antigenicity makes them ideal candidates for cellular therapies [11,12]. Additionally they express molecular markers of pluripotent stem cells including octamer-binding protein 4 (OCT-4), SRY-related HMG-box gene 2 (SOX-2), and Nanog[8].

Ectodermal Derivatives

The ability of hAECs to differentiate to neural cells was demonstrated by Sakuragawa and coworkers in 1996[13]. Studies conducted in animal models have shown that hAECs can promote neural cell differentiation, reduce secondary neural damage associated with inflammation and apoptosis in spinal cord injury [14,15]. It can also promote re-myelination and sprouting of nerve fibers whilst improving functional recovery[16-20]. Their ability to synthesize catecholamines including dopamine (DA) has explored the possibility of hAEC serving as a donor for transplantation therapy of Parkinson's disease (PD)[21]. Furthermore researches have shown that hAEC significantly suppressed splenocyte proliferation *in vitro* and has the potential to attenuate multiple sclerosis (MS) in mouse models[22].

Endodermal Derivatives

Studies have demonstrated expression of hepatocyte-related genes in hAEC such asalbumin, α1-antitrypsin etc. Cultivated hAEC has also demonstrated albumin production, glycogen storage, and albumin secretion consistent with the hepatocyte gene expression profile[23]. Hence hAEC represent a noncontroversial source of cells for liver-based regenerative medicine[24,25]. HAEC can also be induced to differentiate in to pancreatic β-cells. It has been demonstrated that multiple such genes including insulin, pancreas duodenum homeobox-1, paired box gene 6, NK2 transcription factor-related locus 2, Islet 1, glucokinase, and glucose transporter-2 are expressed in these differentiated progenitors. Scientists have also discovered that these cells release C-peptide in a glucose-regulated manner in response to extracellular stimuli.These findings indicated that hAEC might be a new source for cell replacement therapy in type 1 diabetes[26,27].

Mesodermal Derivatives

It has been shown that freshly isolated hAEC express cardiac-specific transcription factor GATA4; cardiac-specific genes such as myosin light chain (MLC)-2a, MLC-2v, cTnI, and cTnT; and the α-subunits of the cardiac-specific L-type calcium channel (α1c) and the transient outward potassium channel (Kv4.3). Upon stimulation with basic fibroblast growth factor (bFGF) or activin A these cells have shown to express Nkx2.5, a specific transcription factor for cardiomyocytes, and a cardiac-specific marker, atrial natriuretic peptide (ANP). Co-culture experiments have confirmed that hAEC cells are able to both integrate into cardiac tissues and differentiate into cardiomyocyte-like cells[28-31]. HAEC also expresschondrocyte related genes, including SOX-9, SOX-5, SOX-6, bone morphogenetic proteins (BMP)-2 and -4, as well as BMP receptors. Recent studies have shown that implanted hAECs aid in cartilage repair in porcine models[32]. One study has demonstrated that in vitro induction of viable human amnion expresses cartilage-specific markers and accumulates GAGs within the biomatrix[33].

Conclusion

Owing to its tri-lineage differentiation potential hAEC are a versatile cell population that can be easily harvested and propagated in to a desired tissue type or a disease model.

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