Physiology and Pharmacology

Physiol Pharmacol 20 (2016) 1-4

www.phypha.ir/ppj

Letter to Editor

Low pH preconditioned amniotic epithelial cells for stem cell therapy of cancer

Hassan Niknejad[1,2]*, Ghasem Yazdanpanah[1], Mona Kakavand[2], Yasaman Lavaie[2]

1. Department of Tissue Engineering and Regenerative Medicine, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Nanomedicine and Tissue Engineering Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Amniotic epithelial cells (AECs) possess unique characteristics, which make them a suitable source for cell-based therapeutic strategies. AECs have stem cell properties with low-immunogenicity (due to expressing HLA-G molecule and absence of MHC class I and II antigens) and no ethical problems, as well as availability in sufficient numbers, which can be obtained from a placenta. We have recently shown that the AECs have anti-cancer properties due to inhibition of angiogenesis, induction of apoptosis and cell cycle arrest probably through inhibition of HSP90. Since the viability of AECs must be improved after in vivo administration in acidic microenvironment of tumor, we clarify here that low pH preconditioning of AECs would lead to more survival of implanted cells in tumor site as well as improved functional outcomes.

Keywords:
Amniotic membrane;
Epithelial cells;
Preconditioning;
Cancer;
Stem cell therapy

Received: 16 Jan 2016
Accepted: 13 Mar 2016

***Correspondence to:**
H. Niknejad
Tel: +98-21-22439848
Fax: +98-21-22439847
Email:
niknejad@sbmu.ac.ir
niknejadh@yahoo.com

Introduction

Amniotic epithelial cells (AECs), the innermost cell layer of placenta, are in direct contact with amniotic fluid during pregnancy (Peirovi et al., 2012). The AECs have low immunogenicity, anti-fibrotic and anti-bacterial properties (Tehrani et al., 2013; Kakavand et al., 2015), as well as stem cell characteristics (Niknejad et al., 2013a), which make them suitable for using in a variety of clinical fields. We have shown recently that amniotic membrane and amniotic cells have anti-cancer property (Niknejad et al., 2013b; Niknejad et al., 2016). AECs possess anti-tumor characteristics due to induction of apoptosis and cell cycle arrest in cancer cells and also inhibition of angiogenesis (Seo et al., 2008; Niknejad et al., 2014; Niknejad and Yazdanpanah, 2014). Soluble factors secreted from cultured AECs induce apoptosis in cancer cells (Niknejad et al., 2014). Inhibition of heat shock protein-90 is probably responsible for anti-cancer property of the AECs (Niknejad et al., 2013d). In addition, amniotic cells secret anti-neoplastic soluble factors such as interferon-γ, interleukin-2, 3, 4, and 8, tumor necrosis factor-β, transforming growth factor-β, macrophage colony-stimulating factor, granulocyte macrophage colony-stimulating factor, and granulocyte chemotactic protein (GCP-2) (Niknejad et al., 2012; Mamede et al., 2014). Furthermore, the cells cycle is arrested in G1/S

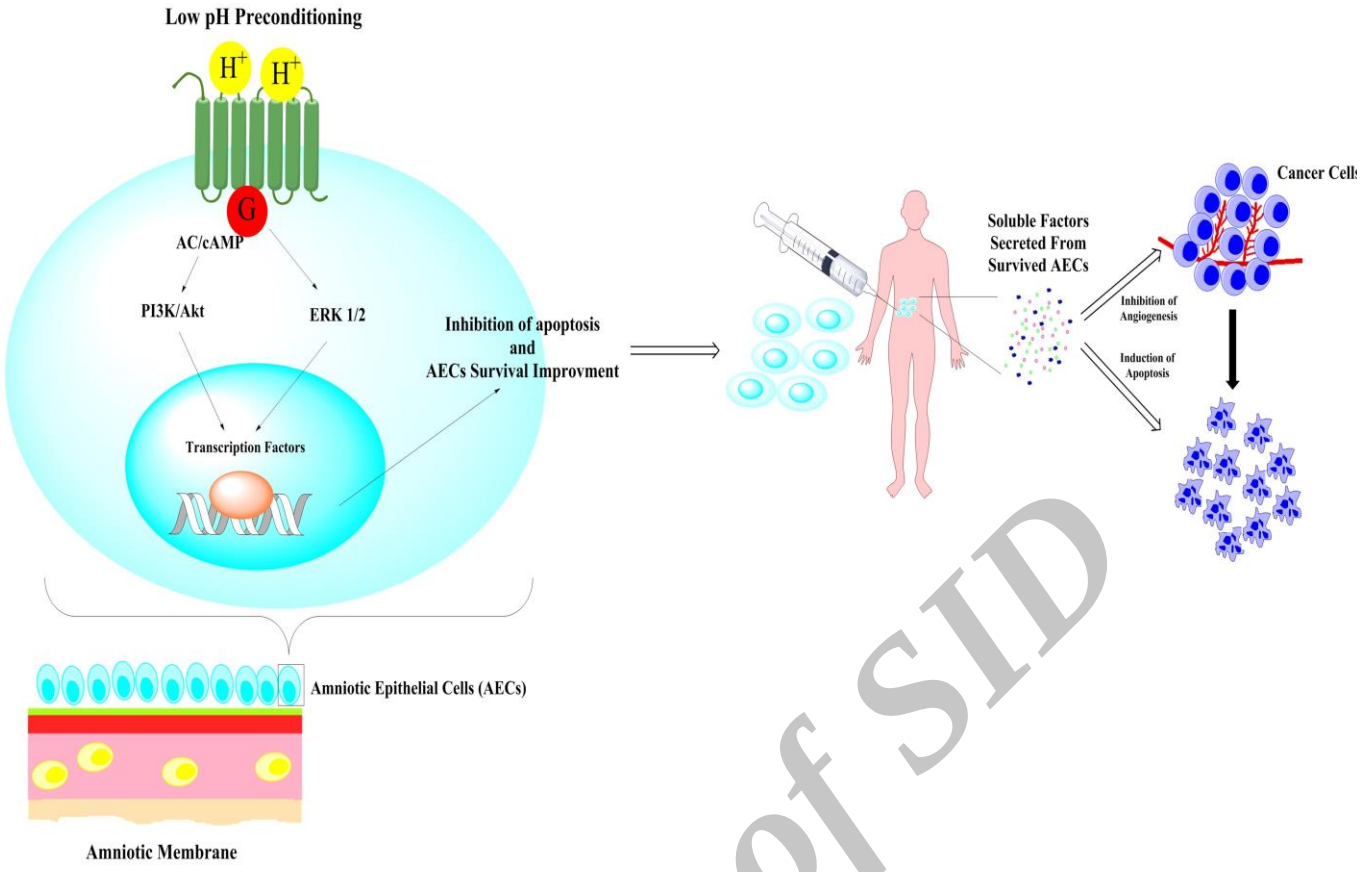

Fig.1. Low pH preconditioning of the amniotic epithelial cells leads to more survival of these cells after injection into tumor microenvironment. Low pH (high concentration of H^+) activates G-protein coupled receptors (GPCRs). GPCRs activate adenylyl cyclase (AC) that produces cAMP with further activation of PI3K/Akt pathway. GPCRs also activate ERK1/2 pathway. PI3K/Akt and ERK1/2 pathways lead to transcription of genes associated with improvement in survival and inhibition of apoptosis. AECs with prior preconditioning secrete anti-cancer soluble factors in injected tumor site, which results in induction of apoptosis in tumor cells and inhibition of angiogenesis.

phase after treatment of cancer cells with amnion-derived cells condition media (Magatti et al., 2012). AECs produce and release some chemicals, which inhibit capillary formation and decrease both the number of vessel sprout and vessel length. AECs express some anti-angiogenic factors including thrombospondin-1, endostatin and heparin sulfate proteoglycan (Yazdanpanah et al., 2015). Also, amniotic cells contain all four tissue inhibitors of metalloproteases (TIMP-1, -2, -3 and -4), which have potent anti-angiogenic effect (Niknejad et al., 2013c). Based on these evidences, AECs have been targeted for cell-based therapy of cancer.

The successful employment of stem cells for cell replacement therapies has been limited by poor survival rate of the cells following implantation. Significant decrease of cell survival and induction of apoptosis occur following injection of the cells and reduce the effectiveness of stem cell therapy, with some estimating about 90% cell loss within 24 hours of implantation (Abraham and Gerstenblith, 2007). Several approaches have been developed to overcome this problem, in which cellular preconditioning and reprogramming prior to implantation into pathological sites (using physical, chemical, genetic, and pharmacological manipulation of the cells) have demonstrated promising results that “prime” the stem cells to the “state of readiness” (Haider and Ashraf, 2010). Preconditioning stem cells prior to implantation to diseased or damaged tissue has been shown to increase implanted cell survival as well as to improve functional outcomes.

Acidic pH is a major characteristic of tumor microenvironment, which could affect survival of the cells transplanted for inhibition of cancer progression. Since AECs have been targeted for cell therapy of cancer, we suggest here that low pH preconditioning of amniotic cells could survive and inhibit apoptosis of cells after injection in tumor microenvironment. The acidic preconditioning protocols are depending on the

type of cell, pH of cell culture medium and incubation time. In the majority of studies, the cells were preconditioned in the pH range of 6.5 to 7.1 for about 24 hours before any further examinations (D'Atri et al., 2011; Cencioni et al., 2013; Mena et al., 2014). However, this protocol must be adjusted for each individual cell line to obtain optimal results.

Preconditioning of AECs in low pH medium leads to activation of G-protein coupled receptors (GPCRs), which induce cell survival intracellular signaling. GPCRs activate adenylyl cyclase (AC) and further production of cAMP that results in activation of PI3K/Akt signaling. Moreover, the GPCRs positively influence the ERK1/2 signaling pathway. Both PI3k/Akt and ERK1/2 signaling activate transcription factors responsible for anti-apoptotic and survival genes' expression (Okajima, 2013). The survived AECs could secrete soluble factors that induce apoptosis of cancer cells and inhibit angiogenesis in tumor site. The schematic illustration of above idea (which is based on the literature) is shown in Figure 1.

Consistent with this idea, the studies have found that acidic milieu is harmful for transplanted hematopoietic progenitor cells (CD34+) and the control and maintenance of physiologic pH via a combination of certain cytokines and cAMP donors improve cell viability and function (D'Atri et al., 2011). Moreover, Cencioni et al showed that acidic preconditioning induced therapeutic potential of bone marrow ckit+ cells through nitric oxide dependent up-regulation of CXCR4 (Chemokine (C-X-C Motif) Receptor 4) (Cencioni et al., 2013). Low pH preconditioning also has capability to increase viability and proliferation of endothelial colony-forming cells by inhibition of p38 signaling (Mena et al., 2014).

In conclusion, low pH preconditioning of amniotic epithelial cells would be helpful to preserve cell viability and to improve functional outcomes in acidic microenvironment of tumors (probably through up-regulation of transcription factors responsible for anti-apoptotic and survival genes' expression); a strategy which might be useful in the effort to optimize transplant protocols in regenerative medicine.

References

Abraham MR, Gerstenblith G. Preconditioning stem cells for cardiovascular disease: An important step forward. Circ Res 2007; 100: 447-9.

Cencioni C, Melchionna R, Straino S, Romani M, Cappuzzello C, Annese V, et al. Ex vivo acidic preconditioning enhances bone marrow ckit+ cell therapeutic potential via increased cxcr4 expression. Eur Heart J 2013; 34: 2007-16.

D'Atri LP, Etulain J, Romaniuk MA, Torres O, Negrotto S, Schattner M. The low viability of human cd34+ cells under acidic conditions is improved by exposure to thrombopoietin, stem cell factor, interleukin-3, or increased cyclic adenosine monophosphate levels. Transfusion 2011; 51: 1784-95.

Haider H, Ashraf M. Preconditioning and stem cell survival. J Cardiovasc Transl Res 2010; 3: 89-102.

Kakavand M, Yazdanpanah G, Ahmadiani A, Niknejad H. Blood compatibility of human amniotic membrane compared with heparin-coated eptfe for vascular tissue engineering. J Tissue Eng Regen Med 2015.

Magatti M, De Munari S, Vertua E, Parolini O. Amniotic membrane-derived cells inhibit proliferation of cancer cell lines by inducing cell cycle arrest. J Cell Mol Med 2012; 16: 2208-18.

Mamede AC, Laranjo M, Carvalho MJ, Abrantes AM, Pires AS, Brito AF, et al. Effect of amniotic membrane proteins in human cancer cell lines: An exploratory study. J Membr Biol 2014; 247: 357-60.

Mena HA, Lokajczyk A, Dizier B, Strier SE, Voto LS, Boisson-Vidal C, et al. Acidic preconditioning improves the proangiogenic responses of endothelial colony forming cells. Angiogenesis 2014; 17: 867-79.

Niknejad H, Deihim T, Peirovi H, Abolghasemi H. Serum-free cryopreservation of human amniotic epithelial cells before and after isolation from their natural scaffold. Cryobiology 2013a; 67: 56-63.

Niknejad H, Khayat-Khoei M, Peirovi H. Inhibition of mmps might increase anticancer properties of amniotic epithelial cells. Med Hypotheses 2012; 78: 690-1.

Niknejad H, Khayat-Khoei M, Peirovi H, Abolghasemi H. Human amniotic epithelial cells induce apoptosis of cancer cells: A new anti-tumor therapeutic strategy. Cytotherapy 2014; 16: 33-40.

Niknejad H, Khayat-khoei M, Yazdanpanah G, Peirovi H. Evaluation of cytotoxic effects of condition medium from amniotic epithelial cells on cancer cell lines hela and mda-mb-231. Physiology and Pharmacology 2013b; 17: 156-163.

Niknejad H, Paeini-Vayghan G, Tehrani FA, Khayat-Khoei M, Peirovi H. Side dependent effects of the human amnion on angiogenesis. Placenta 2013c; 34: 340-5.

Niknejad H, Yazdanpanah G. Anticancer effects of human amniotic membrane and its epithelial cells. Med Hypotheses 2014; 82: 488-9.

Niknejad H, Yazdanpanah G, Ahmadiani A. Induction of apoptosis, stimulation of cell-cycle arrest and inhibition of angiogenesis make human amnion-derived cells promising sources for cell therapy of cancer. Cell Tissue Res 2016; 363: 599-608.

Niknejad H, Yazdanpanah G, Mirmasoumi M, Abolghasemi H, Peirovi H, Ahmadiani A. Inhibition of hsp90 could be possible mechanism for anti-cancer property of amniotic membrane. Med Hypotheses 2013d; 81: 862-5.

Okajima F. Regulation of inflammation by extracellular acidification and proton-sensing gpcrs. Cell Signal 2013; 25: 2263-71.

Peirovi H, Rezvani N, Hajinasrollah M, Mohammadi SS, Niknejad H. Implantation of amniotic membrane as a vascular substitute in the external jugular vein of juvenile sheep. J Vasc Surg 2012; 56: 1098-104.

Seo JH, Kim YH, Kim JS. Properties of the amniotic membrane may be applicable in cancer therapy. Med Hypotheses 2008; 70: 812-4.

Tehrani FA, Ahmadiani A, Niknejad H. The effects of preservation procedures on antibacterial property of amniotic membrane. Cryobiology 2013; 67: 293-8.

Yazdanpanah G, Paeini-Vayghan G, Asadi S, Niknejad H. The effects of cryopreservation on angiogenesis modulation activity of human amniotic membrane. Cryobiology 2015; 71: 413-8.