Properties and Therapeutic Potential of Human Amniotic Membrane

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ABSTRACT

Worldwide a lot of people suffering from massive burns, skin defects/diseases and surgical wound associated skin dysfunctions each year require rapid amniotic grafts. Amniotic Membrane (AM) has been employed in the treatment of wounds for almost 100 year; beginning with early application of AM obtained from labor and delivery to various types of burns and wounds. Amniotic membrane is rich in collagen and growth factors that support the healing process. The avascular, low immunogenic, anti-inflammatory, anti-scarring and wound healing properties of amniotic membrane make it valuable in a wide range of regenerative medicine applications. Nowadays, AM has become an important source of stem cell as well. Amniotic membrane is a promoter of epithelialization and is a non-tumorigenic tissue and its use has no ethical problems. Because of its attractive properties, AM has been applied in several surgical procedures related to ocular surface reconstruction and the genito-urinary tract, skin, head and neck, among others. So far, the best known and most auspicious applications of AM are ocular surface reconstruction, skin applications and tissue engineering. Here, we provide an overview of the properties and therapeutic potential of AM.

Key words: Amniotic membrane, wound healing, allograft, immune-privileged, anti-inflammatory, epithelialization

INTRODUCTION

Throughout the world, non-healing wounds impart significant challenges on both the people affected and their healthcare providers. When wounds fail to heal with standard therapies over a reasonable period of time, clinicians may select advanced modalities, such as Amniotic Membrane (AM) with a clear scientific rationale to promote accelerated healing. The avascular, low immunogenic, anti-inflammatory, anti-scarring and wound healing properties of amniotic membrane make it valuable in a wide range of regenerative medicine applications. Amniotic Membrane (AM) is a gift of nature which not only protects the fetus inside the womb but also has several medicinal properties. It serves as natural barricade to protect the fetus from bacterial infection and trauma. Application of AM in the treatment of disease has been started in 1910 (Davis, 1910). It is widely used in skin substitution (Bujang-Safawi et al., 2010), treatment of acute Stevens-Johnson syndrome (Gregory, 2011), chronic leg ulcer treatment (Tehrani et al., 2013). In addition, use of AM in ocular burn treatment first documented in 1940’s (Sorsby et al., 1947; De Rotth, 1940). Pain, electrolyte abnormalities and bacterial infections are reduced when it is used
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in burn dressing while increase the rate of re-epithelialization (Adly et al., 2010). Amnion membrane acts as a scaffold for proliferation and differentiation due to the presence of fibronectin, elastin, nidogen, collagen types I, III, IV, V and VI, elastin and hyaluronic acid (Tehrani et al., 2013; Mohammad et al., 2000; Riau et al., 2010; Higa et al., 2005). Another important advantage of using AM in allotransplant or xenotransplant is lack of immunogenicity. Histocompatibility antigens HLA-A, B or DR are absent in AM which proves its lack of immunogenicity (Shimazaki et al., 1998). Promotion of epithelialization, anti-inflammatory properties, anti-fibrotic properties, antibacterial properties and anti-angiogenic properties are confirmed by the presence of several related factors (Malhotra and Jain, 2014) that makes AM is an ideal therapeutics for burns and wound healing. Now a day, amniotic membrane has become an important source of stem cell as well, because epithelial and mesenchymal cells isolated from AM shows expression of several important stem cell markers. For this reason AM has become important part of tissue engineering (Niknejad et al., 2008). Given these background, in this literature review, we aimed to discuss the properties and therapeutic application of AM.

STRUCTURE OF AMNIOTIC MEMBRANE

Amniotic membranes develop from extra-embryonic tissue and consist of a foetal component (chorionic and amnion) and a maternal component (decidua). These two parts are held together by the chorionic villi and connect the cytotrophoblastic shell of the chorionic sac to the decidua basalis. The foetal component separates the foetus from the endometrium. The amniochorionic membrane forms the outer limits of the sac that encloses the foetus, while the innermost layer of the sac is the AM. Thickness of normal AM is in between 0.02-0.05 mm (Malhotra and Jain, 2014). From histological perspective AM is an avascular, thin and tough transparent membrane (Agarwal et al., 2014). Amniotic membrane is composed of three major layers: (a) Epithelium, a single layer of metabolically active cuboidal and columnar cells which are in direct contact with amniotic fluid, (b) Basement membrane and (c) A mesenchymal layer (Parolini et al., 2008; Ilancheran et al., 2009). The mesenchymal layer is further divided into compact, fibroblast and spongy layer (Agarwal et al., 2014). Amniotic membrane contains two distinct types of cells with different embryonic origin: embryonic ectoderm derived Amniotic Epithelial Cells (AECs) and mesoderm derived Amniotic Mesenchymal Cells (AMCs) (Benirschke and Kaufman, 2000; Blackburn, 2003). The major components that contribute to the integrity of AM and its biochemical properties are: cytoskeletal proteins of AM epithelial and stromal cells, e.g., actin, tubulin, different cytokeratins, vimentin, desmin; junctional proteins between AM epithelial cells, e.g., occludin, claudin-3 and -4 and desmoplakin and different types of collagen I, III, IV, V, VI hyaluronan and proteoglycans, which are abundant in AM stroma (Cirman et al., 2014).

PROPERTIES OF AMNIOTIC MEMBRANE

Several properties of AM allow its application in the treatment of burns, wound and ocular surgery. These include: (a) Promotion of epithelialization (Lee and Tseng, 1997), (b) Anti-angiogenic effect (Hao et al., 2000), (c) Anti-scarring effect (Liechty et al., 2000), (d) Anti-inflammatory effect (Hao et al., 2000), (e) Presence of growth factor (Koizumi et al., 2000), (f) Antimicrobial effects (Inge et al., 1991), (g) Expression of stem cell markers (Niknejad et al., 2008) and (h) Low immunogenicity (Hori et al., 2006).

PROMOTION OF EPITHELIALIZATION

Basement membrane of AM is composed of collagen type IV, V and VII which meticulously resembles to the conjunctival and corneal basement membrane. It facilitates the growth of
epithelial cells (Malhotra and Jain, 2014). This basement membrane facilitates epithelial cell migration (Fukuda et al., 1999; Meller et al., 2002; Meller and Tseng, 1999), strengthens basal epithelial cell adhesion (Keene et al., 1987; Sonnenberg et al., 1991), promotes differentiation of epithelial cell (Guo and Grinnell, 1989; Kurpakus et al., 1992) and prevents apoptotic cell death (Boudreau et al., 1996) in case regeneration of corneal epithelium. Above mention properties of AM appreciate its use in the treatment of epithelial defects of ocular surface.

**ANTI-ANGIOGENIC AND ANTI-SCARRING EFFECT OF AM**

Angiogenesis is the formation of new blood vessel from pre-existing one. Some specific compounds have been detected in AM which can prevent angiogenesis. Anti-angiogenic chemicals identified in both epithelial and mesenchymal cells of AM are thrombospondin-1, endostatin and all four types of tissue inhibitors of metalloproteases (TIMP-1, 2, 3 and 4) (Hao et al., 2000; Rowe et al., 1997). Scar tissue formation is a common phenomenon in normal wound healing process. Biological process of scar formation is complex and mediated by cell-cell interaction and cell-matrix interaction of cytokines. Mainly inhibition of TGF$\beta$ signal transduction is attributed to anti-scarring effect of AM (Lee et al., 2000). Tseng et al. (1999) showed that expression of transforming growth factor beta isoforms (TGF$\beta$-1, 2 and 3), TGF$\beta$ type II receptor and myofibroblast differentiation were suppressed in cultured human corneal and limbal fibroblasts by amniotic membrane matrix. Thus AM inhibits conjunctival, corneal and limbal fibroblast proliferation and myofibroblast differentiation. This finally results in scar reduction after ocular surface reconstruction and pterygium surgery (Lee et al., 2000). Scarring, i.e., fibrosis is a common end-point of postnatal wound healing following a variety of pathological insults. It involves complex biological processes mediated by cell-cell and cell-matrix interactions via cytokines.

**ANTI-INFLAMMATORY EFFECT OF AM AND GROWTH FACTOR**

In addition to anti-scarring properties AM also possesses anti-inflammatory effect. Inhibition of expression of certain pro-inflammatory cytokines from damaged ocular surface such as interleukin (IL) 1a, IL-2, IL-8, tumor necrosis factor-\(\beta\), interferon-\(\gamma\), basic fibroblast growth factor and platelet derived growth factor is attributed to AM’s anti-inflammatory effect (Solomon et al., 2001). Both amniotic epithelial and mesenchymal cells express interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1RA), these cytokines can suppress inflammatory process by their own mechanism (Hao et al., 2000). In previous study it has been proved that, IL-10 can suppress the effect of pro-inflammatory cytokine IL-6 (Fortunato et al., 1996) and tumor necrosis factor-alpha (Fortunato et al., 1997). The IL-10 also suppresses the production of IL-8, a pro-inflammatory chemokine which attracts migration of neutrophils (Fortunato et al., 1998). Amniotic membrane also contains inter-a-trypsin inhibitor which also possesses anti-inflammatory action (Na et al., 1999). Another important pro-inflammatory cytokine of AM is IL-1RA. IL-1RA is a potential inhibitor of IL-1. By inhibiting IL-1, IL-1RA inhibits the inflammatory action mediated by IL-1 (Romero et al., 1994). High molecular weight glycosaminoglycan (hyaluronic acid) present in AM serves as a ligand for CD4, thus prevents adhesion of inflammatory cells including T lymphocytes to the AM stroma (Dua et al., 2006). Amniotic membrane can also suppress the staffing of inflammatory cell such as polymorphonuclear cells, CD3 cells, CD4 cells, T cells and CD11b cells to the wounded site thus decreasing inflammation (Higa et al., 2005; Wei et al., 2003). These anti-inflammatory attributes of AM are advantageous for the treatment of chronic wound.
Several studies on human amniotic membrane confirmed the presence of some important growth factor. Presences of EGF, TGFα, HGF, KGF, bFGF, TGF-β1 and TGF-β2 have been confirmed by RT-PCR and ELISA (Koizumi et al., 2000). Nerve Growth Factor (NGF) has also been determined in human amniotic epithelial cells (Sakuragawa et al., 2001).

**ANTIMICROBIAL EFFECTS OF AM**

Activity against microorganism is an important property of AM. Amniotic membrane contains natural antimicrobial molecules which are component of innate immune system thus act as safeguard against Gram negative and Gram positive bacteria, viral an fungal infection (Espinoza et al., 2003; King et al., 2007). The β-defensins are an important group of antimicrobial peptides which resist microbial colonization, expressed in amniotic epithelial cells. Beta 3-defensin is the most prevalent defensin of AEC (Buhimschi et al., 2004). Some other important antimicrobial components expressed in AM are low molecular mass elastase inhibitor, secretory leukocyte proteinase inhibitor and elafin (Agarwal et al., 2014). Reduction in bacterial count has been detected in burn patients treated with AM (Robson and Krizek, 1973). In several study activity against Streptococcus, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* has been shown (Tehrani et al., 2013; Kjaergaard et al., 1999, 2001).

**EXPRESSION OF STEM CELL MARKER**

As mentioned previously, both epithelial and mesenchymal cells isolated from amniotic membrane express stem cell markers associated with human embryonic stem cells. In several studies it has been confirmed that AECs express stem cell markers such as, OCT-4, Sox-2, FGF-4, Rex-1, CFC1, Nanog, DPPA3, PROM1, PAX6, SSEA-3, SSEA-4, Tra 1-60, Tra 1-81 and GCTM2 by different techniques including RT-PCR, FACS and immunocytochemistry (Parolini et al., 2008; Marongiu et al., 2010; Diaz-Prado et al., 2010; Moodley et al., 2010; Miki et al., 2005; Ilancheran et al., 2007). On the other hand, AMCs also express stem cell marker such as, SSEA-3, SSEA-4, OCT-4, Rex-1 and BMP-4 detected through RT-PCR, FACS and immunocytochemistry (Ilancheran et al., 2009; Bilic et al., 2008). Clonogenicity is the ability of a single cell to form a cloned colony and is a key defining function that reveals the self-renewal properties of stem cells. The AECs have clonogenic capabilities and in some cases it can be compared to some HESC lines (Niknejad et al., 2008).

**LOW IMMUNOGENICITY**

Immunogenicity is an important factor in any type transplantation. In case of AM transplantation immune acute rejection does not occur. Because AECs do not express HLA-A,-B,-D and-DR antigens on the cell surface, but express HLA-G (Hori et al., 2006). It is also reported revealed that expression of HLA-G is up-regulated in conjunctival and limbal epithelial cells when these cells are cultured on uncovered AM (Higa et al., 2006). Though immunogenicity of AM is controversial, it is thought that AM has low immunogenicity. It is also found that immunogenicity of cryopreserved AM is less than fresh AM (Niknejad et al., 2008). Food and Drug Administration (FDA) approved several methods of AM processing such as Delbeco Modified Eagle Medium (DMEM) or cryopreservation in 50% glycerol, these two methods cause death of AECs thus leading to non-immunogenicity (Kruse et al., 2000). Another immunosuppressive phenomenon of AM is to suppress T lymphocytes in allografted limbus cells, thus increasing the rate of successful grafting (Ueta et al., 2002).
Amniotic membrane as a scaffold for tissue engineering: Biocompatibility of scaffold is the most important precondition for tissue engineering. Biocompatibility refers to the property of being biologically compatible which should not produce any toxic, injurious, carcinogenic, mutagenic or immunological response in living tissue (Weiss et al., 2008). In addition to biocompatibility, AM confirms adequate mechanical properties (permeability, stability, elasticity, flexibility and resorbability), desired cell adhesion, delivery of bio-modulatory components e.g., growth factors and genetic materials (Baguneid et al., 2006; Yang et al., 2001). Attachment of cells to a scaffold is greatly affected by the components of extracellular matrix (ECM) of the scaffold. Adhesion and growth of the overlying stem cells is greatly influenced by presence or absence of certain ECM component e.g., collagen, laminin, fibronectin and vitronectin within any basement membrane. In addition to allowing attachment of cells migration and molecules on ECM serve as adhesion ligands that transmit signals via their interaction at cell surface receptors (Niknejad et al., 2008). It has been shown that epithelial and mesenchymal cells on amnion scaffold are highly interconnected and capable of penetrating the porous structure of scaffold and this method is frequently used in ocular surface and skin reconstruction (Yang et al., 2001, 2006; Fatima et al., 2006). Cultivation of endothelial cells on scaffold created from AM is also reported as a possible approach for vascular TE (Capeans et al., 2003).

AMNIOTIC MEMBRANE IN OPHTHALMOLOGY

AM has gained a distinctive place in ophthalmic surgery and is now widely used in many parts of ocular surface reconstruction. Amniotic membrane can also promote epithelialization of denuded areas of ocular surface (Tsai et al., 2007). Amniotic membrane can be used in the treatment of persistent epithelial defects as a single layer or multilayer graft depending on the depth of lesions providing a substrate for epithelial cells to migrate and adhere to the basement membrane. Rates of success of using AM for PED’s treatment may vary from 64-91% (Lee and Tseng, 1997; Hopkinson et al., 2006). Multilayer AM is used to treat non-traumatic corneal microperforation and descemetoceles with a success rate of 72.7-82.3%. In this case AM affords architectonic support, substitution of collagen for corneal stroma and anti-inflammatory and anti-fibrotic actions which terminate progressive tissue degradation (Letko et al., 2001; Hanada et al., 2001). Several studies suggested that AM can also be used in non-healing infective ulcers of ocular surface due to bacteria, fungi virus and protozoa because AM possesses inhibitory effects on several proteolytic enzymes secreted by these microorganisms (Malhotra and Jain, 2014). Partial Limbal Stem Cell Deficiency (LSCD) can be treated with AM to restore ocular surface by promoting epithelialization and reducing inflammation which maximizes functioning of remaining limbal stem cells (Solomon et al., 2002; Tseng et al., 1998). After removal of large conjunctival lesions and conjunctival benign and malignant tumors including Ocular Surface Squamous Neoplasias (OSSN), tumor, patients with a scarred conjunctiva or where the conjunctiva needs to be preserved, AM can be used to reconstruct the surface of the conjunctiva. Because AM can provide a healthy basement membrane as well as maintains the normal goblet cell containing phenotype of these cells (Anderson et al., 2001; Prabhasawat and Tseng, 1997). It is also reported that AM can be used to reduce scarring at the time of filtering surgery, to repair early or late leaks in case of glaucoma (Paridaens et al., 2001).

AMNIOTIC MEMBRANE IN BURN HEALING

As mentioned previously, application of AM in dressing of burns and wounds started in the early of 20th century. AM has several properties such as non-immunogenicity, bacteriostatic
characteristics, anti-inflammatory, anti-angiogenesis, preventing collagen degradation and promoting epithelialization which make AM an ideal biological skin substitute for the treatment of burn (Fujishima et al., 1998). Andonovska et al. (2008) showed that, use AM provide significantly better result than conventional method in the treatment of dermal and sub-dermal burns (Gabric et al., 1999). Gruss et al. (1978) performed an experiment of 120 patients with ulcers, elective surgical wounds, infected wounds, contaminated surgical wounds, nonhealing or poorly healing wounds, burns and traumatic soft tissue wounds and got excellent wound coverage with some distinct advantages over other biological dressings (Andonovska et al., 2008).

AMNIOTIC MEMBRANE IN PERIODONTICS

In addition to above mentioned application AM has also found application in the field of periodontics. Some recent papers showed that, AM provides satisfactory result in terms of increased tissue thickness, root coverage and increased attached gingival tissue, excellent appealing results in terms of texture and color match, barrier for intra-bony defects and furcation contribution as well as intraoral soft and hard tissue healing (Gruss and Jirsch, 1978; Velez et al., 2010; Adachi et al., 2014; Samandari et al., 2004; Rosen, 2013; Holtzclaw et al., 2013; Gurinsky, 2009; Rinastiti et al., 2006). Cryopreserved AM was evaluated for tissue healing in case of pain, epithelialization, lesion size, infection, inflammation and scarring during dental implant surgery. In this trial AM was found to be effective in helping cicatrisation, supporting growth of epithelium, wound healing, reinforced adhesion and reducing pain of patients (Gruss and Jirsch, 1978). Another study concluded that AM used for gingival wound healing can induce rapid epithelialization and both granulation of tissue and collagen formation while suppress inflammation (Gurinsky, 2009). Intraoral alveolar wounds with bone exposure during vestibuloplasty of reconstructed mandible have been treated successfully using hyperdry amniotic membrane (Rinastiti et al., 2006).

CONTROVERSIES AND LIMITATIONS

As mentioned in mechanism of action AM has several properties which make it useful for treatment of wound, burn and ocular surface. But still there have some contradiction due to the presence of some contradictory biomolecules in AM. This is not astonishing in biological tissue as well as in AM, balances and counterbalances would be needed for action of those biomolecules. Nevertheless, when applied in burn treatment or ocular surgery only the presence of wanted molecules for certain mechanism of action is mentioned without regarding to the conflicting molecules. As for instance, prostaglandin present in AM may promote inflammation but presence of prostaglandin inactivating enzyme and secretory leukocyte inhibitor can suppress inflammation (Dua et al., 2006; Tsuno et al., 2014; Cheung et al., 1990). Anti-inflammatory cytokines IL-1Ra and IL-10 present in AM can suppress inflammation but IL-6 and IL-8 can promote inflammation. Likewise, amniotic membrane harbors various growth factors e.g., EGF, which supports epithelial growth and TGF supports wound healing. But TGF itself enhances formation of scar tissue and becomes contrary to the proposed anti-scarring effect of AM in preventing conjunctival and corneal healing. Both TIMPS and TMPS are present in AM. TIMPS prevent vascularization while TMPS promote vascularization (Smieja et al., 1993).

CONCLUSION

Amniotic membrane is being used in the field of medicine over 100 years ago. Still now, it is a better option and has tremendous potential in regenerative medicine due to having stem cell
properties. Optimization of controversial effects of AM can lead to better results. Recent advances in tissue preservation techniques have resulted in commercially available amniotic membrane products for use in the clinical setting. Available data suggest that these products promote rapid and complete healing of chronic wounds. Although there are limited data available regarding most amniotic membrane-based products, there is substantial preclinical and clinical evidence supporting the rationale and effectiveness of dehydrated human amnion/chorion membrane allograft as a treatment modality. However, before using AM in burn or wound healing, ocular surgery and surface reconstruction strict precautionary and safety criteria should be taken. Potential contributors need to be screened efficiently for risk factors associated with diseases transmission. A medical records must be analyzed to ensure free of risk factors and clinical proof of HIV, hepatitis B and C, syphilis, cytomegalovirus (CMV) and other possible infections should be carried out (Chopra and Thomas, 2013). Any preservation technique which can impair the properties of AM should not be used. Ongoing and future studies will further define and establish the value of amniotic membrane for the treatment of other types of wounds and regenerative medicine applications.

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