REVIEW ARTICLE

Pleiotropic Properties of Amniotic Membrane for Modulation of Periodontal Healing

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ABSTRACT

Human amniotic membrane (HAM), composed of inner most layers of placenta i.e. amnion and chorion, is widely used in medical field especially in ophthalmology. It is a composite membrane consisting of pluripotent cellular element embedded in a semipermeable membranous structure. It has been shown that amniotic membrane has anti-inflammatory, anti-scarring, antimicrobial and excellent revascularization properties. AMs is an excellent membrane for reconstructive surgery because it is easily accessible, ethically acceptable, easy to use, and easily stored without alteration to its therapeutic properties. This review article explains the inherent structure, properties, mechanisms and the potential applications of HAM for healing of periodontal wound.

KEYWORDS: Amniotic Membrane, Periodontal Treatment, Wound Healing

INTRODUCTION

Wound Healing is a complex and dynamic process involving numerous cell types (epithelial and endothelial cells, lymphocytes, fibroblasts, etc.) and an array of soluble factors (e.g. growth factors, cytokines, etc.). This tightly orchestrated process involves various cellular events that often overlap one another. A more complex situation presents itself when a mucoperiosteal flap is opposed to an instrumented root surface deprived of its periodontal attachment.[1,2] In this case, the wound margins are not two opposing vascular gingival margins but comprise the rigid nonvascular mineralized tooth surface, on the one hand, and the connective tissue and epithelium of the gingival flap, on the other.[1]

Stem cells therapy is emerging as a powerful tool to generate biological substitutes and regenerate for damaged tissue with high proliferability, differentiability and function. The incorporation of these cells in the periodontal wound may therefore accelerate the periodontal healing.[1,3] Many efforts are under way to develop novel bioengineered wound-healing products, and include involvement of MSCs in the wound-healing process.[3]

Amniotic membrane (AM) has been used as skin substitute for several decades due to its pleiotropic effects for enhancing wound healing cascade. Amnion-derived cells with multipotent differentiation ability have attracted a lot of attention in tissue engineering, cell-transplantation therapy and periodontal regeneration.[4,5] The purpose of this review

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article is establishment of a platform regarding inherent structure, properties and mechanisms that support the physiological roles of the amnion membrane in the regeneration of oral and periodontal tissues.

BASIC STRUCTURE OF AMNION MEMBRANE

AM is the innermost lining of the fetal membrane that is in contact with the developing fetus; serving as a natural barrier to protect the fetus from infections and trauma because of the lack of a fetal immune system. From embryological aspect AM develop from extra-embryonic tissue and consist of a foetal component (the chorionic plate) and a maternal component (the deciduas). At histological level AM is a thin, tough, transparent, avascular composite membrane composed of three major layers: a single epithelial layer, a thick basement membrane, and an avascular mesenchymal layer. The amniotic epithelial cell layer is a single layer of flat, cuboidal and columnar cells that are in direct contact with the amniotic fluid consisting mainly of collagen.[6,7]

At ultrastructure level mesenchymal layer can be further divided in to compact, fibroblast and spongy layer. Two types of cells, with different embryological origins, present in AM; one is amniotic epithelial cells (AECs) derived from embryonic ectoderm and amnion mesenchymal cells from embryonic mesoderm.[8,9] The extracellular matrix mainly consists of collagen (types I, III, IV, V, VI), laminins, reticular fibers, proteoglycans, glycoproteins, cell-signaling proteins (such as cytokines), and growth factors that are essential to the healing process. There are no nerves, muscles, or lymphatics in the amniotic membrane; instead, the nutrients it requires are supplied directly by diffusion out of the amniotic fluid and/or from the underlining decidua. [10]

HISTORICAL ASPECT

Successful applications of human AM in various clinical and surgical fields had been reported for over 100 years.[11,12] The first documented use of AM is as a skin substitute by Davis in 1910.[13] The first evidence in ophthalmology was made by De Rotth and the usage of human AM in ophthalmic practice was propelled further by Kim and Tseng.[14] It has been also used in maxillofacial surgery for mouth floor reconstruction after a glossectomy by Kothary and for maxillofacial defect reconstruction by using pure pectoralis muscle flap lines by Lawson.[15,16] Subsequently the foetal membrane was found to be useful in the management of burns; creation of surgical dressings; as well as reconstruction of the oral cavity, bladder, and vagina; tympanoplasty; arthroplasty and so forth.[17]

ANTI SCARRING AND ANTI INFLAMMATORY PROPERTIES

Fibroblasts are naturally responsible for scar formation during wound healing and are activated by transforming growth factor β (TGF- β). The AM down-regulates TGF-β and its receptor expression by fibroblasts and in doing so, reduce the risk of fibrosis. Therefore, an AM scaffold can modulate the healing of a wound by promoting tissue reconstruction rather than promoting scar tissue formation.[18,19]

There are several reports in the literature regarding the anti-inflammatory property of AM. Stromal matrix of AM decrease the secretion of proinflammatory cytokines like IL-1α , IL-1β, tumor necrotic factor-alpha (TNF-alpha) and interferon (IFN) while simultaneously increasing the production of anti-inflammatory cytokines interleukin IL-10 and IL -4, tissue inhibitors of metaloproteinase

(TIMPs-1,2,3,4) as well as endostatin which inhibits endothelial cell proliferation, angiogenesis, and tumor growth.[20,21] Hyaluronic acid is a high molecular-weight glycosaminoglycan that exists in large quantities in the AM and acts as a ligand for CD44, which is expressed on inflammatory cells and plays an important role in adhesion of inflammatory cells, including lymphocytes, to the AM stroma.[22] AM also reduces recruitment of various inflammatory cells including polymorphonuclear cells, CD3 cells, CD4 T cells, and CD11b cells to the injured site thereby reducing the inflammation. Various immune cells like T cell, dendritic cell and B cell are actively suppressed that prevents pathological remodeling and excessive fibrosis.[23,24] These anti-inflammatory properties of AM are beneficial for the treatment of chronic wounds like oral ulcers, herpetic lesions, and healing after any surgical procedures. The facilitation of lipid peroxidation and apoptosis of keratinocytes (programmed cell death) is also reported.[25]

ANTIMICROBIAL EFFECT

The β-defensins are a major group of anti-microbial peptides that are expressed at epithelial cells of AM and are an integral part of the innate immune system by resisting the microbial colonization.[26,27] The β3-defensin is the predominant defensin in the amniotic epithelium.[28] In addition, low-molecular-mass elastase inhibitors, secretory leukocyte proteinase inhibitor (SLPI) and elafin, are expressed in the AM.[28,29] Elafin and SLPI both have antimicrobial and act as components of the innate immune system to protect related surfaces from infection.[30] Many bactericidal products of purine metabolism and lysozyme are also found in the amnion membrane. Lactoferrin is a globular multifunctional protein, which has both anti-microbial and anti-inflammatory effects, by serving as an antioxidant and an iron chelator in tissues;[31] it also suppresses the production of interleukin-6 in the amniotic fluid during amniotic infection.[32] An antiviral agent, cystatin E, the analogue of cysteine proteinase inhibitor is also present in AM.[29,32]

Due to its excellent mechanical property AM forms early physiologic "seal" (firm adherence barrier with the host tissue), via fibrin and elastin linkages, precluding bacterial contamination.[33] This tight adherence helps in restoring lymphatic integrity, protects circulating phagocytes from exposure and allows faster removal of surface debris and bacteria, prevents dead space formation and serous discharge accumulation, prevents hematoma formation reducing microbial accumulation and thereby the risk of infection.[34]

IMMUNOGENESITY

Low risk of immunogenicity is an important component of creating a biocompatible scaffold for TE. Although the immunogenicity of the AM is controversial, in general, it is believed that the AM possesses low immunogenicity.[35] However, In addition, immunogenicity of cryopreserved AM tissue is less than that of fresh AM tissues and that cryopreserved cells are expected to be nonviable. This approach guides some researches to use of cryopreserved AM instead of fresh AM.[36] FDA approved methods of amniotic membrane processing include Delbeco modified eagle medium (DMEM) or cryopreservation in glycerol 50%, both of which result in the death of all amniotic epithelial cells leading to nonimmunogenicity.[37] Human amniotic membrane has the ability to suppress T lymphocytes in allografted limbus cells, this implies immunosuppressive properties which can increase the success rate of grafting.[38]

INCREASE VASCULARIZATION OR REVASCULARIZATION

Studies have clearly demonstrate that dehydrated human amnion contain a large number of pro-angiogenic growth factors, including angiogenin, angiopoietin-2, endothelial growth factor, insulin derived growth factor, and Vascular endothelial growth factor. These signals also stimulated human microvascular endothelial cells to proliferate in vitro, and further, to increase production of a number of endogenous growth factors, cytokines, and receptors related to angiogenesis.[39,40] This angiogenic potential helps in the development of tissue engineered vascular grafts which are useful in revascularization of ischemic tissues, chronic ulcers, repair of bone and cartilage. Furthermore, AM tissue promoted chemotactic migration of human endothelial cells in vitro, suggesting that these soluble factors are capable of recruiting endothelial cells to promote wound re-vascularization.[41]

MECHANICAL PROPERTIES

Differentiation of some progenitor cells depends on mechanical stimulus/signals, therefore, scaffold must create adequately stiff environment throughout the site where new tissue is desired.[3] Increase stiffness enhances the stability of scaffold, and prevent displacement that leads to uninterrupted healing as well as feasibility in exchange of metabolic products of involving cells during early phase of healing. Scaffold should also have sufficient elasticity for maintaining the shear stresses of surrounding tissue. Collagen and elastin in ECM provide stiffness and elasticity for AM respectively.[41,42] The mechanical response of AM is time dependent that is termed as viscoelastic in nature. [43,44]

THE AMNIOTIC MEMBRANE AS A SCAFFOLD FOR TE

AM successfully completed the prerequisite for choosing as a scaffold for tissue engineering. AM has biocompatibility, low immunogenicity, adequate mechanical properties (permeability, stability, elasticity, flexibility, resorbability), good cell adhesion, and easy delivery of biomodulatory agents such as growth factors and genetic materials.[45-47] The attachment of a cell to a scaffold is largely affected by the components of the scaffold's extracellular matrix (ECM). The presence or absence of certain ECM molecules such as collagen, laminin, fibronectin and vitronectin within any basement membrane has a huge influence on the adhesion and growth of the overlying stem cells. As well as allowing the cells to attach and migrate, the ECM molecules also serve as adhesion ligands, which transmit signals *via* their interaction at cell surface receptors. When epithelial and mesenchymal cells are seeded on a cellular scaffold created from the AM, the cells were highly interconnected and capable of penetrating the porous structure of the amnion scaffold. Cultivation and seeding of epithelial cells on an amnion scaffold is a frequently used method for ocular surface and skin reconstruction.[48-50] And lastly, cultivation of endothelial cells on an AM scaffold has also been reported as a potential approach for vascular TE.[51]

CHALLENGES WITH AMNIOTIC MEMBRANE

Precautions and safety criteria regarding transmission of infectious diseases are always associated with AM. Potential donors need to be identified effectively for any risk factors; malignant, autoimmune, and neurologic conditions; and social habits and other exposures to definitively determine its

suitability for human transplantation.3 A screening of relevant medical records to ensure freedom from risk factors for and clinical evidence of HIV, hepatitis B, hepatitis C, Cytomegalovirus, syphilis, and other possible infections, should be carried out.[52] The comprehensive mapping of foetal membranes at term, detected an unique area termed as "zone of altered morphology" (ZAM) includes structural weaknesses and a marked disruption of the connective tissue layers as well as a marked reduction of the thickness and cellularity of the membrane due to cells death and degradation of basement membrane by MMPs.[53,54] Due to disturbed anatomy and histology use of the ZAM is not preferred.

APPLICATION IN PERIODONTICS

AM has found application in various fields of medicine, including management of burns; reconstruction of the oral cavity, bladder and vagina; tympanoplasty; arthroplasty, opthalmology and so on.[11,12,34,54] Recently, this multipurpose tissue has found application in the field of periodontics.

Recent literature indicates that the AM provides good results in terms of root coverage, increased tissue thickness, and increased attached gingival tissue, excellent esthetic results in terms of texture and color match, as barrier membrane for intrabony defects and furcation involvement as well as intraoral soft and hard tissue healing.[55-62] The minimal thickness of this barrier membrane, combined with its self-adherent nature, allows ACM to intimately adapt to contours around roots and over defects; this eliminates the need for sutures, making the procedure less technically demanding and significantly decreasing surgical time. The ability to self-adhere makes processed dehydrated allograft amnion an attractive option for multi-teeth procedures and recession defects in particularly hard to reach areas such as the molar region.[58,59,60]

Velze et al. [55] evaluated cryopreserved AM for tissue healing in terms of lesion size, epithelialization, pain, infection, inflammation, and scarring during dental implant surgery. Their trial showed that cryopreserved AM was effective in helping cicatrisation, wound healing, supported the growth of the epithelium, reinforced adhesion, and decreased the pain of subjects.

Adachi et al.[56] reported an analysis of Periodontal ligament cells obtained from maxillary third molar, cultivated on AM to determine the distribution of factors responsible for maintaining the characteristics of PDL. The immunofluorescent and electron microscopic findings suggested a improved proliferation of PDL cells with lateral conjugation and adhesion to AM as well as maintenance of their inherent properties with strong cell-cell adhesion structures (desmosomes and tight junctions) to adjacent cells. Samandari et al.[57] investigated the effects of amniotic membrane (AM) in bone induction and wound healing after vestibuloplasty surgery on animal samples. Our study findings indicate that the AM is a suitable cover for different injuries and acellular AM has the potential for rapid improvement and bone induction. AM has also used as a barrier membrane for the promising regenerative management of class III furcation involvement in combination with composite allograft.[58] A recent retrospective observational report documented the use of AM for combination GTR treatment of periodontal intrabony defects. The postoperative observations showed improved density of radiographical bone fill as compared to base line level. There are some inherent benefits of placental barrier (AM) over conventional GTR membrane.[59] Evidences are also present regarding the use of AM for the purpose of gingival recession. Placental barrier (AM) may provide an effective alternative to

autograft tissue treatment for root coverage procedures.[60] A histological study demonstrated that amniotic membrane transplantation for gingival wound healing may induce rapid epithelialization and both granulation tissue and collagen formation but suppress inflammation.[61] Tsuno et al. have successfully treated intraoral alveolar wounds with bone exposure during vestibuloplasty of the reconstructed mandible with the use of hyperdry amniotic.[62]

CONCLUSION

This article paves a way for future studies that may investigate the application of AM for periodontal regeneration and repair. More studies exploring the potential of this allograft in periodontal therapies are required.

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