Biomaterials in Veterinary World – With an Emphasis on Wound Management

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Abstract
Wound healing based on the concept of tissue engineering is an emerging technique in regenerative medicine. Tissue engineering follows the principles of cell transplantation, material science and engineering toward the development of biological substitutes that can restore and maintain normal function of the defective area. Tissue engineering strategies generally fall into two categories: the use of acellular extracellular matrices, which depend on the body’s natural ability to regenerate for proper orientation and direction of new tissue growth and the use of matrices seeded with expanded cells. Acellular tissue matrices are typically prepared by removing cellular components from tissues by mechanical and chemical manipulation to produce collagen rich extra cellular matrices. Natural collagenous materials are being investigated for wound repair because of inherent low antigenicity and their ability to integrate with surrounding tissue.

Key words: Wound, Biomaterial, Collagen, Tissue Engineering

Introduction
Wound
Damage or loss of the integrity of skin caused by skin or cutaneous wound may impair the skin functions at various extents ranging from significant disability to even death (Tsuruta et al, 2002; Kaustabh et al, 2007). Skin wound can arise from mechanical trauma, surgical procedures, reduced blood circulations, burns, or aging (Allgower et al, 1995). The wound healing process, in dermal or other tissue sites, involves a series of complex biochemical events that take place in a sequential manner, although they overlap in time. These biochemical events— the inflammatory, proliferative, and maturation or remodelling phase—are integral to effective wound healing (Fossum et al, 2007). The wound healing process can lead either to fibrotic tissue replacement (scarring) with limited functional restoration or to natural tissue restoration, particularly in healing by second intention. Most skin wounds can heal naturally, but
additional surgery necessitates immediate coverage using skin substitutes to aid repair and regeneration when there is extensive or irreversible damage to the skin (Balasubramani et al., 2001).

**Protective substitutes**

Synthetic and biological protective substitutes are currently used in clinical applications. In large defects, synthetic substitutes act as temporary wound coverage until definitive reconstruction is performed (Schallberger et al., 2008). Biological-derived substitutes have been advocated for their ability to more effectively promote granulation and epithelialization of dermal wounds than synthetic ones. Biological-derived wound dressings effectively regulate evaporation and exudation and effectively protect the wound site from bacterial infection. It is most urgent for such extensive skin wound therapy to provide the outmost barrier i.e. epidermal coverage in order to prevent infection, reduce water/blood loss and control pain. However, an epidermal coverage alone often fails to restore the structure and functions of the skin and problems such as fragility of the graft, wound contraction and scar formation often occurs (Williamson et al., 1994; Hafemann et al., 1999; Carsin et al., 2000). Usually, dermis and hypodermis could not regenerate easily after injury (Pomahac et al., 1998; Falanga et al., 2007). Increasingly, apparent evidences demonstrate that effective wound healing always necessitates the presence of the dermis layer in the skin substitutes (Ruszczak, 2003; Dai et al., 2004). The re-epithelialization of keratinocytes and take rate are promoted through dynamic dermal – epidermal interactions and hence the graft exhibits higher resistance to wound contraction and scarring. Many natural skin substitutes such as xenografts, allografts and autografts have been used for wound healing. However, these naturally derived skin substitutes cannot accomplish skin regeneration due to limited donor sites, risk of infection, slow healing and association with the formation of scar (Clark et al., 2007; Price et al., 2008). Providing biomaterials at the wound site enhance regeneration of soft tissue and they acts as template for the site of injury.

**Biomaterials for Regenerative Repair**

The biomaterials are materials intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ, or function of the body. In-vitro and in-vivo investigations have sought to develop implantable biomaterials for wound dressing that can ideally integrate into the wound while optimizing dermal and epidermal restoration (Clark et al., 2007). Growth factors and cytokines retained in these materials are also thought to enhance healing (Singer and
Clark, 1999). The restoration of dermis requires three-dimensional scaffolds to provide elasticity and strength to the epidermal graft and feed the keratinocytes in epidermal layer. Hence, one crucial factor in skin tissue engineering is the construction of a tissue scaffold as template to guide restructuring of cells and subsequent host infiltration of the skin graft. Over the past three decades, extraordinary advances and improved understanding in cell/molecular biology have led to achievements in skin tissue regeneration for wound healing. (Falanga et al, 2007)

The modern tissue engineering task is to develop three-dimensional scaffolds of appropriate biological and biomechanical properties, at the same time mimicking the natural ECM and promoting tissue regeneration. The scaffold should permit cell adhesion, infiltration and proliferation for ECM synthesis. Furthermore, it should be biodegradable, bioresorbable and non-inflammatory.

**Decellularization of Biomaterials**

It is well-known that cellular biomaterials are quickly rejected upon implantation. The histocompatibility antigens present on the transplanting cells is responsible for graft rejection in cellular grafts (Gulati and Cole, 1984). Removal of cells (Decellularisation) from a tissue or an organ leaves the complex mixture of structural and functional proteins that constitute the extracellular matrix (ECM). The goal of decellularisation is to ameliorate the antigenicity of the biological graft by efficiently removing all its cellular and nuclear material while minimizing any adverse effect on the composition, biological activity and mechanical integrity of the remaining ECM (Gilbert et al, 2006). Decellularization can be brought about by specific physical, chemical, and enzymatic methods which leave a material composed essentially of extra cellular matrix (ECM) components. These acellular tissues retained their natural mechanical properties and promoted remodeling of the prosthesis by neovascularization and recellularization by the host (Schmidt and Baier, 2000).

**Collagen Rich ECM as Biomaterial**

The primary structural framework for ECM is provided by collagen. Generally, protein based biomaterials mimic extra cellular matrix at the site of injury and help skin regeneration. Among all the protein biomaterials, collagen is a potentially useful biomaterial as it is a major constituent of connective tissues. Its characteristics offer several advantages such as biocompatible and non-toxic in most tissues, cellular mobility, growth and porous nature.
These properties allow a highly vascularized granulation bed formation on the wound. In addition, collagen enhances keratinocytes and fibroblast proliferation which are important in wound healing (Allgower et al, 1995; Tsuruta et al, 2002; Kaustabh et al, 2007).

Collagen-based biomaterials are of the utmost importance for tissue engineering and regenerative medicine. Because of its superior biocompatibility and low immunogenicity, collagen is still the protein of choice for biomaterials preparation. It can be extracted from various tissue sources and assembled in combination with other molecules. It is also used in the laboratory as a decellularized ECM in fundamental studies or as tissue replacement material in medical applications. Most present research is aimed at the optimization of collagen-based biomaterials for medical applications by enhancing mechanical strength, biodegradability or delivery characteristics.

In veterinary medicine, ECM based biological substitutes such as allogeneic peritoneum (Gomez et al, 2004), amnion (Goodrich et al, 2000) and omentum (Lascelles and White, 2001) have been used to treat open wounds in dogs and horses with mixed success.

Collagen rich ECM exists in all tissues and organs but can be harvested for use as a therapeutic scaffold from relatively few sources. The extracellular matrices have been derived from variety of tissues like small intestinal submucosa (Badylak et al, 1989; Kumar, 2010), urinary bladder (Chen et al, 1999; Dewangan, 2010), tendons (Cartmell and Dunn, 2000), ligaments (Woods and Gratzer, 2005), pericardium, diaphragm (Perme, 2009; Kaarthick, 2011), skin (Purohit, 2008), fish swim bladder (Kumar, 2010; Remya, 2012) for tissue engineering.

Rennekampff et al. (1997) observed that acellular dermal matrix could effectively direct the regeneration of normal skin morphology. Erkin et al. (2007) observed the revascularization potential of xenogenic acellular dermal matrix (allogerm) in rats.

DeSagun et al. (2001) judged the efficacy of xenogenic and allogenic acellular dermal matrix in the repair of full thickness skin defects on dorsum of rats on the basis of gross and immunological observations. Cholecyst derived matrix has the necessary mechanical and regenerative properties to suit soft tissue regeneration application (Burugapalli et al., 2007).

In humans, collagen-based dermal substitutes followed by an epidermal autograft, or more recently bioengineered bilayered skin substitutes (Shen and Falanga, 2003) provide the closest product to the ideal wound dressing (Frame et al., 2004).
Small intestinal sub mucosa as collagen rich extracellular matrix significantly reduced the contraction observed in wounds and the wounds developed a healthy epithelial layer covering and had no signs of infection (Brown-Etris et al., 2002).

The small intestinal sub mucosa induction of host tissue proliferation and replacement has been demonstrated in many tissues, including blood vessels (Hiles et al., 1995), urinary tract (Kropp and Chen, 2000) and body wall (Clark et al., 1996). Angiogenesis, abundant host cell infiltration, mitogenesis, and deposition and organization of new host extracellular matrix scaffolds, thought critical to successful tissue replacement, was observed following implantation of small intestinal sub mucosa scaffolds in the urological (Kropp and Chen, 2000).

Maiti et al. (2001) studied the gastric wound healing in rabbits using absorbable suture material prepared from fish intestine collagen. Grossly, the gastric wound was healed by day 15 and did not reveal any irritation, allergy, toxic effect, leakage or discontinuity of suture line in all the test animals. Histologically, complete healing of gastric mucosa and dissolution of suture material on day 30 was observed. Epithelialization with neovascularization across the suture site was also seen and the healing tissue was undifferentiated from normal healing tissue.

Divya and Nandakumar (2006) studied a sustained release chlorhexidine in fish collagen membrane (Periocol) derived from swim bladder of fresh water fishes, in periodontics. Study revealed that the collagen membrane had many advantages like easy adhesion and stickiness, proper wound closure, prevention of fluid and blood loss, protection from micro-organisms, oxygen permeability and better healing of severe burns/wounds.

Acellular swim bladder was recommended for clinical testing in of animals for large skin wounds after success full healing evaluation in rabbit (Kumar, 2010) and rat (Remya, 2012).

**Tissue Engineering Based on Cell Matrix Construct**

Cell–matrix construct based bio-engineering concept can be applied for the combination therapy of extracellular matrix and cells. Here, the expanded cells are seeded onto a scaffold synthesized with the appropriate biomaterial. The ECM slowly degrade on implantation and are replaced and remodeled by ECM proteins synthesized by transplanted or in growing cells. Most current strategies for tissue engineering depend on a sample of autologous cells from the diseased organ of the host. However, for many patients with extensive end-stage organ failure, a tissue biopsy may not yield enough normal cells for expansion and transplantation. In these situations, embryonic and adult stem cells are an alternative source of cells from which the desired tissue
can be derived. The use of native cells and adult stem cells is ethically sound and accepted by all major religions and governments.

Mouse embryo fibroblast seeded acellular pericardium and diaphragm of bovine origin was found to be a potent scaffold for skin wound repair in rats (Kaarthik, 2011). Bone marrow derived mesenchymal stem cell seeded acellular fish swim bladder was successfully used for repair of dermal wound created in rat, with significant immuno modulation (Remya V, 2012).

**Conclusion**

Researches on various treatment modalities for wound healing has evolved and progressed during the past several years with ultimate goal of discovering the ideal technique. In initial days little consideration was given to restore the functionality of the damaged tissue. Nowadays, biomaterials were typically chosen for their ability to restore functional tissue. The advantage of using biomaterial is that the repair mechanisms approach optimal conditions, i.e. it can not only repair but can also regenerate new tissue that is similar to that of the recipient’s. One of the areas for improvement and research is the control of graft rejection. It can be achieved through making the biomaterial acellular and utilizing the ability of stems cells to modulate immune response by seeding stem cells over acellular matrix.

**References**