ISSN 0975 – 2633
Review Article
Arch Pharm Sci & Res Vol 1 No 2 106 - 114 October 2009

Role of Glycosaminoglycans in Wound Healing

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Wound healing is a formation phase of collagenous scar by mechanical and chemical injuries that may results from the release of some factors by wounding tissue. Wound healing mechanism (inflammation, re-epitherialization, matrix formation, and remodeling) is got under the regulation of special mediators that secretes blood platelets, macrophages, lymphocytes and so on. Wound healing has been divided into three main phases; inflammation, proliferation, and tissue remodeling. Glycosaminoglycans (GAGs) are highly sulfated linear polysaccharides that comprised of repeating disaccharides units composed of a hexosamine (D-glucosamine or D-galactosamine) and an uronic acid (D-glucuronic acid or L-iduronic acid) except for keratan sulfate (D-glucosamine and D-galactose). GAGs are a family of molecules that include chondroitin sulfate/dermatan sulfate, heparin/heparan sulfate/acharan sulfate, hyaluronic acid, and keratan sulfate and they are mainly located in the extracelluar matrix. In this review, we discuss the mechanism and roles of GAGs in wound healing.

Key words: wound healing, glycosaminoclycans (GAGs), inflammation, proliferation, tissue remodeling

INTRODUCTION

Wound healing is a complex process involving a series of continuous phase by mechanical and chemical injuries and tissues release some factors at the wounding sites. This event occurs by an interconnected process of regeneration dermal and epidermal tissues that involve the migration, proliferation, adhesion and differentiation of cells[1]. Wound healing is influenced by local and systemic factors of collagen fibers by reducing neovascularization and epithelialization rate under the regulation of special mediator that secreted blood platelets, macrophage, lymphocyte and so on [2]. It is generally composed of three particularly phases; inflammation, proliferation, and tissue remodeling [3].

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PHASE OF WOUND HEALING

1) Inflammation (Immediate to 2-5 days)

When an individual is wounded, a set of events takes place in a predictable fashion to repair the damage. Immediately after injury, wound on skin changes its skin structure with atrophy at edge of wound and contraction of tissue. Hemostasis, consisting of the polymerization, deposition of fibrin (clot formation), and platelet degranulation, is started by a variety of factors [4]. Exposed collagen activates the intrinsic and extrinsic clotting cascades in order to facilitate clot formation and pause of bleeding. The clot, as a reservoir of growth factors and cytokines that forms is made of collagen, platelets, thrombin, and fibronectin, release cytokines and growth factors that starts the inflammatory phase and supports the influx of fibroblasts and keratinocytes [5, 6]. Inflammatory cells, the debris of the tissue and bacteria, release signals that can interfere with the migration of keratinocytes and fibroblasts [7, 8]. During the

inflammatory phase, form of granulation tissue consisting of endothelial cells, macrophages and fibroblasts then start to cover and fill the wound site to restore tissue integrity [9]. Neutrophils and macrophages are the first responders in wound healing: for clearing of invading phagocytic bacteria and debris. They release proteolytic enzymes that can convert wound cytokines to active or inactive forms and can induce substantial tissue damage [10]. Macrophages signal the next phase, which involves fibroblast influx and collagen formation. At the end of the inflammatory phase, bleeding is controlled and the wound bed becomes clean [11].

2) Proliferation (2 days to 3 weeks)

The next phase is the proliferation phase that are composed of tissue regeneration, angiogenesis, arrival of fibroblasts, and the actual generation of new blood supply to the wound site [12, 13, 14]. According to progress of inflammatory phase, keratinocytes from the intact epidermis start to proliferate and migrate over the provisional matrix of the underlying granulation tissue for achieve re-epithelialization [9]. Activated macrophages release fibroblast growth factors that stimulate mitogenesis, chemotaxis, differentiation, and angiogenesis and begin synthesizing a collagen, glycosaminoglycans, proteoglycans and fibronectin (Fig. 1). Then extracellular matrices are synthesized, deposited, and remodeled and fibroblasts are transformed into myofibroblasts for wound contraction [15]. Fibroblasts and endothelial cells recruit proliferation to promote the formation of granulation tissue and new blood vessels [16]. Formation of new blood vessels is a necessary step for healing of wounds. Wound contraction leads to wound closure for shrinks in size to bring the wound margins that involve epithelization, connective tissue deposition, and contraction [17]. Angiogenesis involves the growth of new blood vessels from preexisting vessels for restoring blood flow to tissues after injury [16]. During the phase of angiogenesis a basement membrane consisting of glycosaminoglycans and collagen are deposited. Collagen produced by fibroblasts stimulates cellular migration and contributes to new tissue development [18].

3) Remodeling (3 weeks to 2 years)

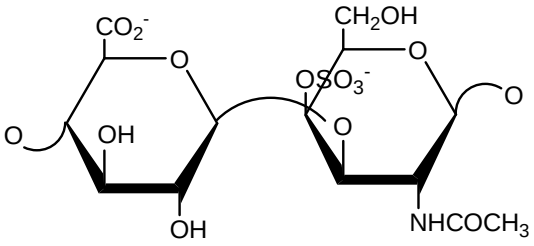
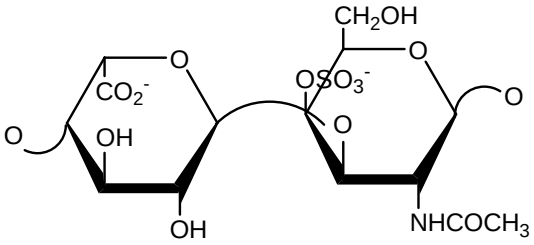
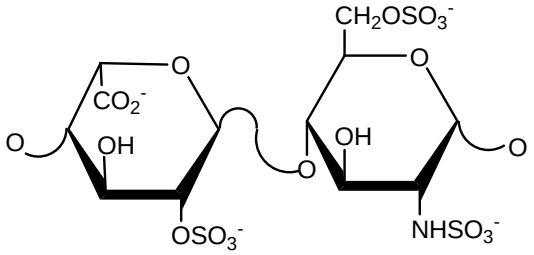
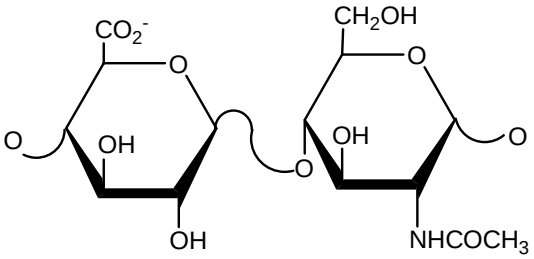
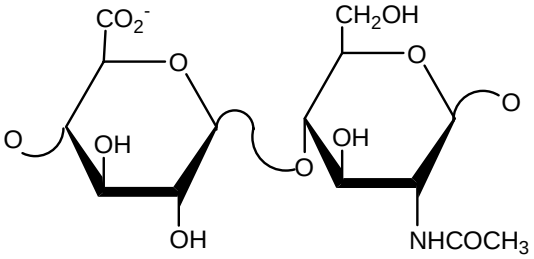
The final phases of wound healing are remodel and maturation of skin. During this stage, macrophages and fibroblasts play important roles for wound remodeling and reshaping of extracellular matrix through cross-linking collagens, cell maturation, and programmed cell death [19]. New collagen is formed until approximately 6 weeks after wounding which increases a tensile strength to wounds in an organized and well-mannered network [20]. Later most of the vessels, fibroblasts, and inflammatory cells slowly disappear through unknown cell death mechanism [21]. Wound strength never returns to 100 percent, because scar tissue is only 80 percent as strong as original tissue at 3 months glycosminoglycans and wound healing.

1. The roles of glycosaminoglycans (GAGs) in wound healing

Glycosaminoglycans (GAGs) are highly sulfated linear polysaccharides that comprised of repeating disaccharides units composed of a hexosamine (D-glucosamine or D-galactosamine) and an uronic acid (D-glucuronic acid or L-iduronic acid) except for keratan sulfate (D-glucosamine and D-galactose) [22, 23]. GAGs are a family of molecules that also include chondroitin

sulfate/dermatan sulfate, heparin/heparan **Table**

Table 1: The structure of glycosaminoglycans

Glycosaminoglycans	Disaccharide unit
Chondroitin sulfate (A type)	
Chondroitin sulfate (B type)	
Heparin	
Heparan sulfate	
Hyaluronic acid	

sulfate/acharan sulfate [24], hyaluronic acid, and keratan sulfate (Table 1). With the exception of hyaluronic acid, other GAGs are covalently attached to core proteins to form of proteoglycans which exist at cell surface, in animal tissues, and in the extracellular matrix [25, 26]. GAGs have been shown to play an important role in keeping homeostasis, for example, wound healing, cell growth and cell-cell interaction and so on.

2.Effects of glycosaminoglycans (GAGs) in

wound healing

During the proliferative phase, fibroblasts synthesize collagen and GAGs that change during the period of granulation tissue for adhesive and no adhesive interactions in matrix [27]. In previous reports, collagen and GAGs complex are used for wound healing. The cross-linking between collagen and GAGs provides enough strength to the tissue during the remodeling phase inhibit the action of collagenase by blocking the cleavage sites of collagen [28]. GAGs bind to collagen with high affinity and GAG-collagen interactions affect the deposition of collagen fibers in vivo [29]. And wound healing mediator, such as IL-8, keratinocyte growth factor, and vascular endothelial growth factor, production by human dermal fibroblasts grown within a collagen-GAG matrix [30]. While wound healing, cell-mediated contraction plays a important role, and therefore collagen-GAG scaffolds reduce wound contraction at wound site [31, 32]. In previous reports, GAGs may help in the formation of a resistant scar and enhanced wound contraction [33] and they are effective during the wound healing phase, for example, reducing the area of skin lesions on UV irradiated rats [34] and effects on epidermal keratinocytes [35, 36].

Hydrogel is a common device used for wound healing experiments. GAGs-hydrogel films as bio-interactive dressing have several advantages; it is beneficial in protecting the wound from bacterial infection and controlling evaporative water loss and permeability of oxygen and carbon dioxide. It also absorbs wound exudates and contributes to enhance the wound healing [37]. And the synthetic extracellular matrix (sECM) hydrogel films composed of co-crosslinked thiolated derivatives GAGs promote wound repair and are the effective delivery devices for basic fibroblasts growth factors (bFGF) that controlled release of bFGF increased neovascularization [38, 39]. In other studies, GAG film stimulates re-epithelialization process that the presentation of growth and differentiation factors and the stimulation and facilitation of cell migration contribute to accelerate wound re-epithelialization [40].

3.Effect of chondroitin sulfate (CS) in wound healing

Chondroitin sulfate (CS) is composed of a repeating sequence of sulfated and/or unsulfated D-glucuronic acid (GlcA) and *N*-acetyl-D-galactosamine (GalNAc) residues linked through alternating β (1→3) and β (1→4) bonds [41]. CS is attached covalently to core proteins in the form of proteoglycans and plays an important role in development of the central nervous system, wound repair, growth factor signaling, and cytokinesis [42, 43, 44, 45]. It has been used clinically for the treatment of chronic diseases such as degenerative arthritis, cirrhosis, and chronic photo damage [46, 47, 48].

CS helps to mediate FGF-2-induced cell proliferation by binding to FGF-2, regulate cell adhesion, and enhances cell spreading and migration through activating focal adhesion growth factor (FAK) and inhibiting Roh A activity [49, 50, 51]. And CS has a stimulating effect to regeneration of flesh wound in case of local single action by both parenteral and local administration [52]. Prepared CS hydrogel plays an important role as a surrogate extracellular matrix, providing as a repository for cytokines and growth factors and provide a structure for fibroblasts and epithelial regeneration [53]. Collagen gels that were cross-linked with chondroitin-6-sulfate (C-6-S) has modified the

normal scarring process and improved the mechanical characteristic of the matrix in wound healing phase [54].

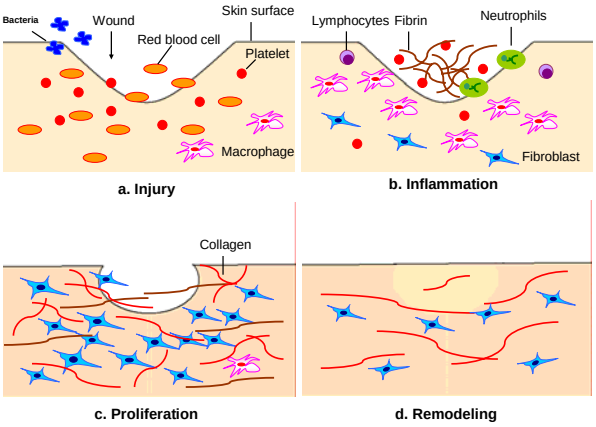


Figure 1. Mechanisms of wound healing

Immediately after injury, wound on skin was changed then formed of clot. During the inflammatory phase, form of granulation tissue consisting of endothelial cells, macrophages and fibroblasts then start to cover and fill the wound site to restore tissue integrity. Macrophages signal the next phase, which involves fibroblast influx and collagen formation. The next phase is the proliferation phase that are composed of tissue regeneration, angiogenesis, arrival of fibroblasts, and the actual generation of new blood supply to the wound site. The final phases of wound healing are remodel and maturation of skin. New collagen is formed until approximately 6 weeks after wounding which increases a tensile strength to wounds in an organized and well-mannered network.

4.Effect of heparan sulfate (HS) and heparin in wound healing

Heparin, a highly sulfated polysaccharide repeat unit composed of L-iduronic acid (Idu) and D-glucosamine (GlcN) and haparan sulfate (HS), a similar structure repeating disaccharide of glucuronic acid (GlcA) and N-acetyl-D-glucosamine (GlcNAc), are synthesized attached to a core protein in the extracellular matrix and the surface [55, 56]. Heparin has an important function as an anticoagulant by forming a complex with antithrombin III and non-anticoagulant effect in carcinoma metastasis and Trousseau's syndrome [57, 58]. In contrast, HS has an important roles in cell growth and development, angiogenesis, viral invasion, and is especially an essential cofactor for FGF-receptor binding [59, 60]. Heparin and collagen mixtures associated with a greater degree of penetration of developing granulation tissue in heparin implants are more vascular in wound sites [61]. Also heparin is associated with prompt and effective endothelial cell repair by increasing capillary circulation and decreasing wound healing time which can promote wound healing [62, 63]. Chitosan/heparin complex used in previous study was nearly completely regenerated with skin appendage structure in the dermis similar to normal skin that effective agent in wound healing [64]. In addition heparin enhances wound healing and restores blood flow by reducing pain and inhibiting clotting and inflammation [65]. Sometimes low molecular weight heparins (LMWHs) are used instead of heparin. LMWHs suppress the early inflammatory phase and increase cellular apoptosis of dermal fibroblasts that is a crucial step in eliminating fibroblasts of healing skin wounds [66]. Also LMWH administration to rats results in important increase of collagen content for wound healing [67].

HS maintains hemostasis, or regulation of blood volume and composition and modulates the activity of the proteases involved in the coagulation cascade as a potent mediators of angiogenesis at the surface of endothelial cells [68]. HS promoted angiogenesis in vivo through removal of HS side chains led to impaired FGF-2 mediated angiogenesis during the proliferative phase of wound healing [69].

5. Effect of hyaluronic acid (hyaluronan, HA) in wound healing

Hyaluronic acid (hyaluronan, HA) is a high molecular weight GAGs that consists of N-acetyl-D-glucosamine and glucironic acid [70]. HA is found in the extracellular matrix (ECM) of soft connective tissues as diverse as the skin, aorta, cartilage and brain [71]. HA plays important role in skin which can effect cell proliferation, differentiation, and tissue repair [72]. Also HA has biomedical advantage that includes ophthalmic surgery, arthritis treatment, wound healing and coating [73].

In many studies, HA affects fetal wound healing that proceeds without the scarring, fibrosis, inflammation or scar formation in contrast with adult wound healing. HA is a important role in structure of the ECM for controls lymphocyte adhesion [74, 75, 76]. And HA has an evident role that modulates proliferation, collagen and protein synthesis of cultured fetal fibroblasts and degradation of fetal wound HA results in increased fibroplasias, collagen deposition, and neovascularization [77, 78, 79].

HA, synthesized by fibroblasts in the early phase of wound healing, provides an aqueous matrix and promotes the migration and proliferation of mesenchymal and epithelial cells [80]. And HA hydrogel films as biomaterials for wound healing drug delivery which controlled drug release based on drug hydrophobicity and act as a local delivery device at wound site [81]. Also, HA reduced initial scar formation and promote of inflammation for enhanced wound healing [82, 83].

CONCLUSION

Wound healing is a complex biological process involving a series of continuous phase by mechanical and chemical injuries, results from the release of some factors by wounding tissue. Recently, the potential roles of GAGs in specific biological processes including angiogenesis [84], tumor growth [85], and bone metabolism [86] have been reported. In this review we highlighted the function of GAGs in wound healing. GAGs are reported to play important roles for promotion of healing processes. The studies of GAGs in wound healing may be a target for future therapeutic approaches in chronic wounds.

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