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REVIEW ARTICLE

Hyaluronic acid: A promising mediator for periodontal regeneration

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ABSTRACT

Hyaluronic acid (HA) is a natural-non sulphated high molecular weight glycosaminoglycan that forms a critical component of the extracellular matrix and contributes significantly to tissue hydrodynamics, cell migration and proliferation. The use of HA in the treatment of inflammatory process is established in medical areas such as orthopedics, dermatology and ophthalmology. In the field of dentistry, hyaluronate has shown anti-inflammatory, antiedematous and anti-bacterial effects for the treatment of gingivitis and periodontitis. Due to its potential role in modulation of wound healing, its administration to periodontal wound sites could achieve comparable beneficial effects in periodontal tissue regeneration and periodontal disease treatment.

Key words:

Key words: Hyaluronic acid, regeneration, periodontal wound healing

Hyaluronic acid is also known as hyaluronan or hyaluronate. It is a high molecular weight polysaccharide (glycosaminoglycan) and plays a vital role in the functioning of extracellular matrices, including those of mineralized and non-mineralized periodontal tissues. It is a critical component of the extracellular matrix and contributes significantly to tissue hydrodynamics, cell migration and proliferation. Hyaluronan is also produced by fibroblasts in the presence of endotoxin; it plays an important anti-inflammatory role through the inhibition of tissue destruction and facilitates healing.[1] The use of HA in the treatment of inflammatory process is established in medical areas such as orthopedics, dermatology and ophthalmology. It has been used in radio-epithelitis,[2] osteoarthritis of the knee[3] and rheumatoid arthritis[4] and cataract surgery.[5] *Rabasseda* reviewed its wide use for the treatment of inflammatory conditions of the knee and temporomandibular joint, which has led to the study of its topical application in the treatment of periodontal diseases.[6]

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In the field of dentistry, preliminary clinical trials have been conducted by Vangelisti and Pagnacco *et al.*[7] in 1997. Hyaluronate has shown anti-inflammatory, anti-edematous and anti-bacterial effects for the treatment of gingivitis and periodontitis. The anti-inflammatory effect may be due to the action of exogenous hyaluronan as a scavenger by draining prostaglandins, metalloproteinases and other bio-active molecules.[8] The antiedematous effect may also be related to the osmotic activity. Due to its acceleration in tissue healing properties, it could be used as an adjunct to mechanical therapy.[9] However, it is conceivable that Hyaluronan administration to periodontal wound sites could achieve comparable beneficial effects in periodontal tissue regeneration and periodontal disease treatment.[1] Hyaluronic acid has been studied as a metabolite or diagnostic marker of inflammation in the gingival crevicular fluid[10] as well as a significant factor in growth, development and repair of tissues.[11]

HISTORICAL BACKGROUND

Hyaluronic acid was discovered in 1934 by Karl Meyer and his colleague John Palmer, scientists at Columbia University, New York, who isolated a chemical substance from the vitreous jelly of cow's eyes.[12] They proposed the name hyaluronic acid as it was derived from Greek word hyalos (glass) and contained two sugar molecules one of which was uronic acid.

STRUCTURE

Hyaluronic acid (HA) is naturally occurring non sulphated

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glycosaminoglycan with high molecular weight of 4,000-20,000,000 daltons. HA structure consists of polyanionic disaccharide units of glucouronic acid and N-acetyl-glucosamine connected by alternating β1–3 and β1–4 bonds [Figure 1]. It is a linear polysaccharide of the extracellular matrix of connective tissue, synovial fluid, embryonic mesenchyma, vitreous humor, skin and many other organs and tissues of the body. Most cells of the body are capable of synthesizing hyaluronic acid and synthesis takes place in the cell membrane. Hyaluronan binds to many other extracellular matrix molecules, binds specifically to cell bodies through cell surface receptors, and has a unique mode of synthesis in which the molecule is extruded immediately into the extracellular space upon formation.[13]

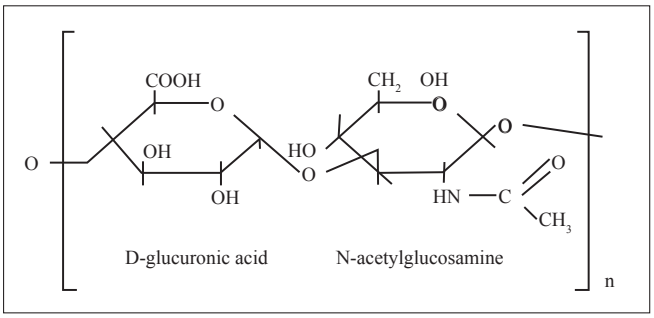

Figure 1: Repeating disaccharide unit of hyaluronan

PROPERTIES

Through its complex interactions with matrix components and cells, hyaluronan has multifaceted roles in biology utilizing both of its physicochemical and biological properties. These biological roles range from a purely structural function in the extracellular matrix to developmental regulation through effects of cellular behavior via control of the tissue macro- and microenvironments, as well as through direct receptor mediated effects on gene expression. Amongst extracellular matrix molecules, it has unique hygroscopic and viscoelastic properties.[14]

Hygroscopic nature

Hyaluronic acid is one of the most hygroscopic molecules known in nature. When HA is incorporated into aqueous solution, hydrogen bonding occurs between adjacent carboxyl and N-acetyl groups; this feature allows hyaluronic acid to maintain conformational stiffness and to retain water. One gram of hyaluronic acid can bind up to 6 L of water. As a physical background material, it has functions in space filling, lubrication, shock absorption, and protein exclusion.[15]

Viscoelastic properties

The viscoelastic properties of the material may slow the penetration of viruses and bacteria, a feature of particular interest in the treatment of periodontal diseases. Hyaluronan as a viscoelastic substance assists in periodontal regenerative procedures by maintaining spaces and protecting surfaces.[15] Through recognition of its hygroscopic and viscoelastic nature, hyaluronic acid can influence the cell function that modify the surrounding cellular and the extracellular micro and macro environments.

FUNCTIONS

Hyaluronan has many structural and physiological functions within tissues, including extracellular and cellular interactions, growth factor interaction and in the regulation of osmotic pressure and tissue lubrication, which help maintain the structural and homeostatic integrity of tissues.[16]

Modulation of inflammation

- In the initial stages of inflammation
- Enhanced inflammatory cell and extracellular matrix cell infiltration into the wound site
- Elevation in proinflammatory cytokine production by inflammatory cells and extracellular matrix cells.
- Organization and stabilization of granulation tissue matrix.
- Scavenges reactive oxygen species, such as superoxide radical (·O_2) and hydroxyl radical (·OH) thus preventing periodontal destruction.
- Inhibition of inflammatory cell-derived serine proteinases.[17]

Stimulation of cell migration, proliferation and differentiation

The remarkable hydrophilicity of the hyaluronic acid makes the coagulum more receptive and thus more likely to undergo colonization by the cells committed to the reconstruction of the damaged tissue by migration, proliferation and differentiation of mesenchymal and basal keratinocytes.[18]

Effect on angiogenesis[19]

Low molecular weight hyaluronic acid has a marked angiogenic effect whereas, surprisingly, high molecular weight has the opposite effect.

Osteoconductive potential[20]

Hyaluronic acid accelerates the bone regeneration by means of chemotaxis, proliferation and successive differentiation of mesenchymal cells. Hyaluronic acid shares bone induction characteristics with osteogenic substances such as bone morphogenetic protein-2 and osteopontin.

Carrier function[21]

Hyaluronic acid may act as biomaterial scaffold for other molecules, such as BMP-2 and PDGF-BB, used in guided bone regeneration techniques and tissue engineering research.

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Bacteriostatic effect[22]

Recent studies on regenerative surgical procedures indicate that reduction of bacterial burden at the wound site may improve the clinical outcome of regenerative therapy. The high concentration of medium and lower molecular weight hyaluronic acid has the greatest bacteriostatic effect, particularly on Aggregatibacter actinomycetemcomitans, Prevotella oris and *Staphylococcus aureus* strains commonly found in oral gingival lesions and periodontal wounds. Clinical application of hyaluronic acid membranes, gels and sponges during surgical therapy may reduce the bacterial contamination of surgical wound site, thereby, lessening the risk of postsurgical infection and promoting more predictable regeneration.

CLINICAL APPLICATIONS IN PERIODONTICS

Hyaluronan has been identified in all periodontal tissues in varying quantities, being more prominent in the nonmineralized tissues, such as gingiva and periodontal ligament, compared to mineralized tissues, such as cementum and alveolar bone. In addition, due to the high levels of hyaluronan in circulating blood serum, it is constantly present in gingival crevicular fluid (GCF) as a serum overload factor. [23]

Natural hyaluronic acid is an extremely hydrophilic polymer; it exists as a viscous gel and does not *per se* have the structural features required for use as a surgical product. An ester of hyaluronic acid synthesized by esterification of a carboxyl group with benzyl alcohol is less water soluble and thus more stable. Because of its unique molecular structure, hyaluronic acid can be assembled into various molecular weights and lyophilized or esterified into a variety of different structural configurations such as sponges and membranes. The rate of biodegradation of these materials can be manipulated by altering their degree of lyophilization or esterification. Thus, hyaluronic acid may be of benefit as a resorbable grafting material in regenerative surgical procedures.[24]

A study by *Yi Xu et al.* [25] concluded that there was no clinical or microbiological improvement achieved by the adjunctive use of Hyaluronan 0.2% gel when compared to mechanical debridement. However in this study Hyaluronan 0.2% gel was applied only once a week for six weeks, a total of seven applications over a six-week period, compared to the recommended application level of three times daily for at least four to eight weeks. The absence of observed clinical improvements, contrary to other published studies, may indicate that the Hyaluronan levels used in this study were well below the optimum levels required to achieve a significant clinical improvement.

Vanden Bogaerde[24] in a recent clinical report evaluated the clinical efficacy of esterified hyaluronic acid in the treatment of infrabony periodontal defects. The author concluded that application of hyaluronic acid seems a promising method for the treatment of infrabony defects by inducing a significant reduction in pocket depth and promoting gain in clinical attachment.

Hyaluronic acid has a multifunctional role in periodontics

- Topical application of subgingival hyaluronic acid gel can be used as an antimicrobial agent as an adjunct to scaling and root planing.[9,26,27]
- Bone regeneration in periodontal bony defects.[24]
- Guided Bone Regeneration.[28]
- Non surgical treatment of peri-implant pockets.[29]
- Peri-implant maintenance of immediate function implants.[30]
- As autologous cell hyaluronic acid graft gingival augmentation in mucogingival surgery.[31]
- As a carrier for newer molecules in various regenerative procedures.[32]
- As a biomaterial scaffold in tissue engineering research.

Safety

Hyaluronic acid is biocompatiable and intrinsically safe to use, with no evidence of cytotoxicity has been found. [33] Hyaluronic acid gel, injections or oral (by mouth), should not be used in patients with allergies.

Adverse effects

Hyaluronic acid side effects although not severe include bruising, swelling, redness, pain, itching and tenderness at the injection site.

Availability

Hyaloss® matrix,[34] trade names of products composed entirely of an ester of hyaluronic acid with benzyl alcohol (HYAFF™), a concentration ranging of from 20 to 60 mg/ml. Hyaloss matrix is a product manufactured as a solid in the form of fibers that forms a gel when hydrated, releasing pure hyaluronic acid for about 10 days. It is highly multipurpose because at room temperature it can form a biodegradable, biocompatible gel that can be adapted by the operator to the desired consistency, by regulating the blood and saline volume.

Gengigel®[9] (Ricerfarma S.r.l., Milano, Italy) contains high molecular weight fractions of Hyaluronic acid in gel formulation with 0.2% concentration for its effect in the treatment of plaque-induced gingivitis as an adjunct to scaling and root planing. The adjunctive use of Hyaluronan with 0.8% after thorough mechanical debridement potentially has major clinical benefits in terms of improved healing after non-surgical therapy.[35]

Gengigel® is available in different presentations to aid treatment efficacy and patient compliance over the longer

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term. It is available as tubes and applicators for use within the surgery, mouthwash and oral sprays for patients to continue treatment at home. Gengigel as a product for oral use has been evaluated by skin irritation test, sensitizing potentiality and percutaneous absorption test and has been proved to be a safe non irritant product.

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