Influence of Hyaluronic Acid in Periodontal Tissue Regeneration

SUMMARY

Hyaluronic acid is a high molecular weight polysaccharide - glycosaminoglycan, which plays a vital role in the functioning of extracellular matrices, including those of mineralized and non-mineralized periodontal tissues. Hyaluronic acid is also important because of its numerous actions in the mechanisms associated with inflammation and the wound healing process.

Hyaluronic acid has been identified in all periodontal tissues in varying quantities, being more prominent in the non-mineralized tissues, such as gingiva and periodontal ligament, compared to mineralized tissues, such as the cement and alveolar bone. Preliminary evidence suggests that hyaluronic acid is a very promising candidate as a mediator of periodontal tissue regeneration and periodontal disease treatment, by promoting a rapid remission of symptoms, not only to the marginal gingiva, but also to the deeper seated periodontal tissues. However, further researches for the therapeutic effects of hyaluronic acid in periodontal disease are essential for realization of true benefits of hyaluronic administration in periodontal tissue regeneration.

Keywords: Hyaluronic Acid; Gingival Inflammation; Periodontal Disease; Periodontal Reparation

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Increasing advances in our knowledge of the mechanism of inflammation and healing process associated with periodontal disease indicated the possible significance of the extracellular matrix components as promoters of periodontal tissue regeneration and healing. Numerous evidence emphasizes the role of hyaluronic acid as a possible candidate in hastening periodontal tissues regeneration.

Structure of Hyaluronic Acid

Hyaluronic acid is a high molecular weight polysaccharide with a molecular weight of 10,000 to 10,000 000 Daltons; this polymer is composed of repeated disaccharide units of N-acetyl glucosamine and D-glucuronic acid and belongs to a family of glycosaminoglycanes, with chemical formula $(C_{14}H_2O NNaO_{11})$ n N-acetyl-D-glucosamine D-glucuronic acid.

Physiology of Hyaluronic Acid

Hyaluronic acid is non sulphurous component, which plays a vital function in the structure and function of the extracellular matrix of several tissues: vitreous corpus, synovial fluid, umbilical cord, synovial joints, skin - where in the presence of 55% is a major component of the basal epidermis and in the mucosa of the oral cavity, including the one in mineralized and non-mineralized periodontal tissues.

Hyaluronic acid has been identified in all periodontal tissues in a different quantity, more present in non

mineralized tissues - gingiva and periodontal ligament, compared to mineralized - cement and alveolar bone[1].

As a result of the high level of hyaluronic acid in the blood serum, it is constantly present in the gingival fluid as a serum factor in large quantities[2,3].

Physiology of Hyaluronic Acid in Gingival Tissue

Endogenous hyaluronic acid is a natural biological substance, which is a major component of the matrix of connective tissue, especially the gingiva. Its interaction with other proteoglycans and collagen gives stability and elasticity of the extracellular matrix of connective tissue. Hyaluronic acid binds to various proteins and water molecules through hydrogen bonds, forming viscous macro aggregate whose primary function is to regulate hydration of the tissues and allows the flow of substances in the interstitial space.

Hyaluronic acid is able to absorb water 50 times more than its normal dry weight. This makes the tissue matrix highly compact and increases exchange and diffusion of small molecules, but also acts as a barrier to diffusion of macromolecules and other invasive substances. When hyaluronic acid binds to cell receptors that are presented only on active defense cells, it acts as a regulator of migration and cellular defense mechanisms that are particularly important in wound healing and tissue repair. Hyaluronic acid probably binds to CD44, heparin-type proteoglycan containing sulphate that is specific for epithelial cells of epithelial-mesenchymal border and regulating reactions between cells and the extracellular matrix, especially their binding with hyaluronic acid. This same type of receptor is involved in the interaction between gingival fibroblasts and T and B lymphocytes, and can speed up the gingival immune response in the presence of pathogenic bacterial flora. Its production rises by bacterial endotoxin stimulation performed on fibroblasts[4,5].

Hyaluronic Acid and Periodontal Disease

Periodontal tissue represents a unique complex where gingival epithelium as non-mineralized and other mineralized tissues formed union at cement-enamel junction (CEJ)[6]. Maintaining the integrity of the union is essential in providing an effective barrier against microbial invasion and preventing the destruction in the deeper periodontal tissues, such as periodontal ligament, cement and alveolar bone from bacterial toxins, enzymes, etc. Structural integrity of the union has been lost by the

chronic inflammation associated with periodontal disease in which such developments have harmful effects on the components of the extracellular matrix of the deeper periodontal tissues, including collagen, proteoglycans and hyaluronic acid. Clinical studies indicate that hyaluronic acid in chronic inflamed gingival tissue undergoes extensive degradation to low molecular products, which reduces hyaluronic function, whereas related sulphurized glycosaminoglycans, as hondroitin4-sulfate and dermatan sulfate, remain relatively intact[7,8]. Primarily responsible for degradation of hyaluronic acid in these cases are thought to be bacterial enzymes - hyaluronidases[9].

The growing number of evidence also suggests additional role of cellular reactive oxygen species, as superoxide radicals (O_2-) and hydroxyl radicals (OH), obtained during hyaluronic destruction in periodontal disease[10-12].

Hyaluronic acid and Periodontal Regeneration

Hyaluronic acid has more structural and physiological functions in tissues, including extracellular and cellular interactions, interactions with "growth" factors and regulation of osmotic pressure and tissue lubrication, which helps in maintaining the structural and homeostatic integrity of tissues[13]. Hyaluronic acid is a key component of chronic injuries during wound healing processes among mineralized and non-mineralized periodontal tissues, namely in the processes of inflammation, granulation tissue formation and remodelling of the epithelium[14]. Diseased tissue in the early stage of reparation is rich in hyaluronic acid[15,16] with the origin of the extracellular matrix cells (fibroblasts and keratinocytes in the gingiva and periodontal membrane, cementoblasts in cement and osteoblasts in alveolar bone) in the inflamed areas, or derived from vascular blood supply in affected site[1,8,17,18].

Hyaluronic acid has multiple roles in the initial inflammatory stages, such as providing a structural framework, through interaction of hyaluronic acid with fibrin plug, which modulates infiltration of inflammatory cells from extracellular matrix of the host. Hyaluronic acid also induces the production of a series of polypeptide molecules (pro-inflammatory cytokines) from fibroblasts, keratinocytes, cementoblasts and osteoblasts[1,18], which promotes the inflammatory response and consequently stimulates hyaluronic synthesis by endothelial cells of blood vessels[19]. Hyaluronic acid continues to be involved in the activation of inflammatory cells, such as polymorphonuclear leukocytes and macrophage function, including their migration and adherence at the site of injury, phagocytosis and destruction of microbial pathogens[20-22], in order to affect the colonization and

proliferation of anaerobic pathogenic bacteria in the gingival sulci and surrounding periodontal tissue. With somewhat contradictory role, hyaluronic acid can regulate the inflammatory response through removal of reactive oxygen species[8,22-24] that are released by inflammatory cells, which may contribute to stabilization of granulation tissue matrix. Furthermore, hyaluronic acid may indirectly act on the development of inflammation and granulation tissue stabilization, preventing the release of enzymes - proteases of the inflamed cells that break down extracellular matrix proteins as healing progresses[25].

Acid content of hyaluronic acid in non-mineralized tissues, where are chronic changes, increases during subsequent formation of granulation tissue and restoring the epithelium[26-27], which is due to the increased hyaluronic synthesis of fibroblasts and keratinocytes[6]. In mineralized periodontal tissues such as alveolar bone, the phase of granulation tissue is gradually replaced by mineralized callus[18]. During these stages, hyaluronic acid participates in multiple cellular functions, such as promoting the migration of cells from the extracellular matrix in the matrix of the injury, cell proliferation and granulation tissue organization. These developments allow reattachment of basal layer of gingival epithelium to the basal lamina and full maturation of mineralized tissues, resulting in reformation of the union of the tooth surface. In later granulation stage, hyaluronic synthesis stops and the existing hyaluronic acid is depolymerised by host enzymes hyaluronidase, which results in the formation of low molecular compounds and alteration of the granulation tissue composition. This indicated that low molecular hyaluronic fragments formed after subsequent hyaluronidases activity promote formation of blood vessels (angiogenesis) in the lesion, although the precise mechanism of action is still unknown[28-30].

Exogenous Application of Hyaluronic Acid

Participation of hyaluronic acid in control mechanisms of tissue regeneration was an advantage to be used as an exogenous agent with more functional role in the treatment of chronic inflammatory changes. As a consequence of its non-toxicity, biocompatibility and numerous biochemical and physico-chemical features, topic and systemic application of exogenous hyaluronic acid offers beneficial effects in modulation and acceleration of the host response through mechanisms described in numerous medical fields. In systemic administration, hyaluronic acid is distributed in plasma with a half-life of 10 minutes and is metabolized in the liver. After local application plasma concentrations are very low, thus allowing optimal presence of the drug at

the site where have to act[31-33]. Studies in mice and rats showed no acute toxic effects or chronic and reproductive effects at doses up to 200mg/kg.

Indications for application of hyaluronic acid in dentistry are numerous:

1. restoration, healing and gingival tissue regeneration as an integral element in the treatment of gingivitis;

2. addition in periodontal treatment;

3. the treatment of stomatitis;

4. eating irritations and lesions on the gingiva and oral mucous membranes (such as aphthae);

5. irritations caused by dentures, fixed or mobile, or during oral surgery procedures;

6. maintenance of the gingiva when dental implants are placed.

Hyaluronic acid is a natural and safe physiologically important substance that can be used by children during the second dentition, pregnant women and the elderly.

Conclusion

Conducted and published clinical studies have shown good results and a high degree of tolerance and acceptability by patients, which is an indicator of clinical value of hyaluronic acid in the treatment and handling gingival disease[34].

It is evident that it has a more functional role in the treatment of chronic changes, including those that occur during periodontal disease. Preliminary evidence suggests that hyaluronic acid is a promising candidate as a mediator of periodontal tissue regeneration and treatment through promoting rapid remission of symptoms, not only in the area of the marginal gingiva, but in deeper periodontal tissues[35-37]. However, further investigations for therapeutic effects of hyaluronic acid application in periodontal disease are essential for evaluating real benefits of its application and full realization of periodontal tissue regeneration.

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