Hyaluronan and its Potential Role in Periodontal Healing

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Abstract: **Hyaluronan is a natural tissue component, which plays a vital role in the functioning of extracellular matrices, including those of the periodontium. This molecule is also important in relation to the mechanisms associated with inflammation and wound healing. The application of exogenous hyaluronan and hyaluronan-based biomaterials has been successful in manipulating and accelerating the wound healing process in a number of medical disciplines, as evident in ophthalmology, dermatology and rheumatology. It is conceivable that hyaluronan administration to periodontal sites could achieve comparable beneficial effects in periodontal healing and surgery, hence aiding treatment of periodontal disease.**

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Clinical Relevance: **Advances in our understanding of the inflammatory mechanisms and wound healing processes associated with periodontal diseases have led to studies into the potential of numerous extracellular matrix components as promoters of periodontal healing and regeneration. Evidence is presented herein supporting the role of another such matrix component, hyaluronan, as a potential aid to periodontal treatment.**

Hyaluronan is a high-molecular-weight (10 000–10 000 000 Da), non-sulphated polysaccharide component of the glycosaminoglycan family, present in the extracellular matrices of many tissues such as skin, synovial joints and periodontal tissues. Hyaluronan consists of repeating disaccharide units of the sugars *N*-acetylglucosamine and D-glucuronic acid, which, unlike the other glycosaminoglycans of extracellular matrices, does not exist as a structural constituent of proteoglycan molecules[1] (Figure 1).

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Hyaluronan has been identified in all periodontal tissues, being particularly prominent in the non-mineralized tissues such as gingiva and periodontal ligament; it is present in only low quantities in mineralized tissues such as cementum and alveolar bone.[1] In addition, as high levels of hyaluronan are present in circulating blood serum, and as gingival crevicular fluid (GCF) is regarded as a serum-derived product (containing most serum components at concentrations comparable with serum itself), hyaluronan has been identified in nearly all GCF samples analysed.[2,3] However, hyaluronan is absent in GCF samples from patients with acute necrotizing ulcerative gingivitis, owing to the high levels of bacterial enzymic activity (hyaluronidases) associated with this condition. It only reappears in the GCF of such patients following metronidazole treatment and the reduction in bacterial numbers.[3]

HYALURONAN AND PERIODONTAL DISEASE

Periodontal tissues represent a unique system, where epithelial, non-mineralized and mineralized tissues meet at the dentogingival junction.[4] The maintenance of junction integrity is essential in providing an effective barrier against microbial invasion and preventing the destruction of the underlying periodontal tissues such as periodontal ligament and alveolar bone by bacterial toxins, proteases, etc. The structural integrity of the junction, however, is lost during the chronic inflammation associated with periodontal diseases. Such events have detrimental effects upon the extracellular matrix components of the underlying periodontal tissues, including collagens, proteoglycans and hyaluronan.

The high-molecular-weight hyaluronan present in periodontal tissues is synthesized by hyaluronan synthase enzymes (HAS1 and HAS2) in cells from the periodontal tissues (fibroblasts and keratinocytes in gingiva and periodontal ligament, cementoblasts in cementum and osteoblasts in alveolar bone).[5]

Degradation of Hyaluronan

High-molecular-weight hyaluronan undergoes extensive degradation to lower molecular weight products in chronically inflamed tissues, such as

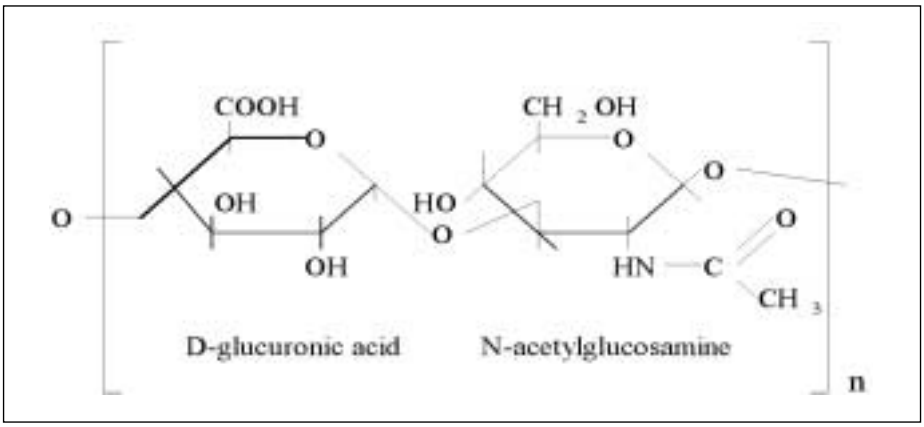

Figure 1. *The repeating disaccharide unit of hyaluronan.*

gingival tissue, which potentially diminishes certain hyaluronan functions. In contrast, the proteoglycan-associated sulphated glycosaminoglycans of periodontal tissues, such as chondroitin 4-sulphate and dermatan sulphate, remain relatively unaffected.[6,7] Low-molecular-weight hyaluronan appears to be particularly prominent in the gingival tissues of patients during the initial stages of periodontitis,[8] possibly as a result of the action of bacterial enzymes (hyaluronidases).[9]

Evidence is also increasingly suggesting a role for reactive oxygen species (ROS), including the superoxide radical ($O_2^{\cdot-}$) and hydroxyl radical ($^{\cdot}OH$) species, in the hyaluronan destruction observed during periodontal diseases.[10] These radicals are generated primarily by infiltrating polymorphonuclear leukocytes and other inflammatory cells during bacterial phagocytosis.[10] Hyaluronan appears to be more susceptible to degradation and modification by these ROS than the proteoglycan-associated sulphated glycosaminoglycans chondroitin 4-sulphate and dermatan sulphate. These findings correlate with the clinical manifestations observed in chronically inflamed gingival tissues described above.[6,7,11,12]

It has further been suggested that the synthesis of low-molecular-weight hyaluronan by another hyaluronan synthase (HAS3) in cells from the periodontal tissues may contribute to the accumulation of low-molecular-weight hyaluronan in chronically inflamed tissues.[5]

HYALURONAN AND PERIODONTAL HEALING

Hyaluronan has many structural and physiological functions within tissues, such as:

- extracellular and cellular interactions;
- growth factor interaction;
- regulation of osmotic pressure and tissue lubrication

which help maintain the structural and homeostatic integrity of tissues.[13]

The molecule is also a key component in the series of stages associated with the wound-healing process in both mineralized and non-mineralized tissues (inflammation, granulation tissue formation, epithelium formation and tissue remodelling).[14,15]

As a consequence of the many functions attributed to hyaluronan during wound healing, advances have been made in the development and application of hyaluronan-based biomaterials in the treatment of various inflammatory conditions.[13] Therefore, based on our knowledge of the multifunctional roles that hyaluronan has in wound healing generally, and the fact that gingival and bone healing follow similar biological principles,[4,14-16] it is conceivable that hyaluronan has comparable roles in the healing of the mineralized and non-mineralized tissues of the periodontium (Figure 2).

Inflammatory Phase

In the early inflammatory phase of repair, tissue is rich in hyaluronan,[17,18] originating from cells derived from periodontal tissues within inflamed sites or derived from the vascular blood supply to the inflamed sites.[1,5,7,18,19]

Hyaluronan has numerous roles in these initial inflammatory stages, such as the provision of a structural framework, via the interaction of hyaluronan with the fibrin clot, which modulates host inflammatory and extracellular matrix cell infiltration into the inflamed site.[20] Hyaluronan also induces the production of a series of polypeptide molecules (proinflammatory cytokines) by fibroblasts, keratinocytes, cementoblasts and osteoblasts,[1,19,21] which promote the inflammatory response and consequently stimulate hyaluronan synthesis by endothelial

1. INFLAMMATORY PHASE
- Prevents periodontopathogen proliferation.
- Enhanced inflammatory cell and extracellular matrix cell infiltration into the inflamed site.
- Elevation in proinflammatory cytokine production by inflammatory cells and extracellular matrix cells.
- Stabilizes granulation tissue matrix.
- Scavenges reactive oxygen species, such as superoxide radical ($O_2^{\cdot-}$) and hydroxyl radical (OH) species.
- Inhibition of inflammatory cell-derived serine proteinases.

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2. GRANULATION PHASE
- Organization of the granulation tissue matrix.
- Extracellular matrix cell proliferation.
- Inflammatory cell and extracellular matrix cell migration.
- Blood vessel formation (angiogenesis).

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3. EPITHELIUM FORMATION
- Migration and proliferation of keratinocytes.

Figure 2. *A summary of the potential roles of hyaluronan in periodontal healing.*

cells.[22] Hyaluronan is further involved in the functioning of inflammatory cells such as polymorphonuclear leukocytes and macrophages, including their migration to the inflamed site, adherence at the inflamed site and the phagocytes and killing of invading microbes.[23–25] Such events would allow counteraction of the colonization and proliferation of anaerobic pathogenic bacteria in the gingival crevice and adjacent periodontal tissues. Hyaluronan itself may also prevent periodontopathogen colonization by directly preventing microbial proliferation.[26]

In a somewhat contradictory role, however, hyaluronan may regulate the inflammatory response, acting as an antioxidant by scavenging ROS from inflammatory cells.[10,25,27,28] Such events may help to stabilize the granulation tissue matrix as, although the overproduction of ROS by inflammatory cells enhances the killing of invading periodontopathogens, their release also has a number of adverse effects such as:

- causing indiscriminate damage to cellular constituents such as DNA, lipids and proteins;
- destroying other extracellular matrix components such as collagens and proteoglycans; and
- altering the metabolism of periodontal cells responsible for extracellular matrix synthesis.[10]

As a consequence of this antioxidant activity and its susceptibility to ROS, hyaluronan is subsequently degraded to lower molecular weight products, as described above. Nevertheless, the degradation and sacrifice of hyaluronan in the granulation tissue matrix via ROS-scavenging may be beneficial in reducing the extent of ROS-induced degradation to other, more structurally significant, extracellular matrix components. More importantly, it may further minimize any potentially detrimental metabolic alterations to the cells from the periodontal tissues.[10] Hyaluronan may also act indirectly to moderate inflammation and stabilize the granulation tissue by preventing enzymes derived from inflammatory cells (serine proteinases) degrading extracellular matrix proteins, as healing progresses.[29]

The Granulation Phase and Re-epithelialization

The hyaluronan content of non-mineralized inflamed tissues is further elevated transiently during the formation of granulation tissue and the re-establishment of the epithelium,[7,30,31] when the granulation tissue phase in mineralized tissues is gradually replaced by a provisional mineralized callus.[15] During such stages, hyaluronan contributes to a variety of cellular functions, such as:

- promotion of extracellular matrix cell migration into the granulation tissue matrix;
- cell proliferation; and
- granulation tissue organization.

Later in the granulation phase, hyaluronan synthesis ceases and existing hyaluronan is depolymerized by host enzymes (hyaluronidases), resulting in the formation of lower-molecular-weight hyaluronan molecules[31] and an alteration in the composition of the granulation tissue. Low-molecular-weight hyaluronan fragments formed following hyaluronidase activity promote formation of blood vessels (angiogenesis) within wound sites, although the precise mechanism of action is unknown.[32-34]

Healing in Foetal Tissue

The hyaluronan content in foetal tissue is more elevated and persists for longer during the healing process than in adult tissue.[14,35,36] The accumulation of hyaluronan in foetal healing has been proposed to accelerate the healing process, via the mechanisms described above, and is thought to be responsible for the relatively scarless nature of foetal wound healing compared with adult wound healing, where excessive fibrotic scar formation is prominent. The mechanism by which hyaluronan enhances the formation of scarless tissue involves a direct effect upon the packing density of deposited collagen fibres. As it has been proposed that sub-populations of gingival and periodontal ligament fibroblasts with foetal-like phenotypes exist within gingival and periodontal ligament tissues,[35] the elevated and prolonged synthesis of hyaluronan by foetal-like fibroblasts may be an important consideration during the progression of periodontal disease and in the potential healing of these periodontal tissues.

HYALURONAN AS A POTENTIAL AID TO PERIODONTAL TREATMENT

It is evident that hyaluronan has a multifunctional role in the wound healing process, with similar mechanisms of healing potentially existing within periodontal tissues. As a consequence of its non-toxicity, biocompatibility and numerous biochemical and physiochemical properties, the use of exogenous hyaluronan or hyaluronan-based biomaterials, applied topically to inflamed periodontal sites, would appear to offer beneficial effects in modulating and accelerating the host response via the mechanisms described. Such benefit has already been demonstrated in a variety of biomedical fields, such as ophthalmology, dermatology and rheumatology.[13,37]

Potential Hyaluronan Periodontal Treatments

The topical application of a high-molecular-weight hyaluronan-based gel (GENGIGEL®) has been proposed to have some potential in inducing periodontal healing in patients with inflammatory gingivitis, during both open and randomized, controlled double-blind studies.[38-40] In preliminary open studies of ten patients (age range 16-54 years) with various forms of gingivitis, eight patients showed clear signs of reduced inflammation within 2 days of GENGIGEL® application, in conjunction with standard oral hygiene regimes, and a ninth within 4 days.[38]

Clinical healing in this study, including post-surgical repair, was reported to occur within a mean time of 6.6 days following application of the gel.[39]

In a preliminary randomized, controlled double-blind study[40] GENGIGEL® or placebo were applied twice daily for 4 weeks, in conjunction with standard oral hygiene regimes, to 60 patients (age range 18-35 years) with gingival pain and bleeding, redness and oedema in the marginal mucosa and interdental papillae, but without deep gingival pockets (<3 mm) (30 treated with GENGIGEL® and 30 with a gel material-only placebo). Patients were assessed at 2 and 4 weeks for approximal plaque index, redness and swelling of the marginal mucosa and the interdental papillae, and sulcus bleeding index. The overall evidence derived from these preliminary studies suggests that the hyaluronan-based gel alleviates marginal gingivitis by significantly reducing scores for redness and oedema in the marginal mucosa and interdental papillae, and by reducing the sulcus bleeding index.

Furthermore, preliminary evidence derived from a randomized, controlled double-blind study also suggests that the topical application of GENGIGEL® is beneficial in accelerating the healing of periodontal wounds following surgery.[41] In this study, GENGIGEL® or placebo were applied twice daily to periodontal wound areas in 32 patients (average age 40 years) for 4 weeks, in conjunction with standard oral hygiene regimes (16 treated with GENGIGEL® and 16 with a gel material-only placebo). Patients were assessed at 8 and 15 days and 3 and 4 weeks. The gel appeared to reduce pain and improve healing rates compared with the placebo. However, these studies have not been quoted in mainstream journals, and further large-scale randomized, controlled clinical trials are required in order to validate the reports fully.

Hyaluronan-based Biomaterials

In addition to the direct beneficial effects of hyaluronan application, a three-dimensional scaffold consisting of the hyaluronan-based biomaterial HYAFF® has also successfully been utilized to support tissue engineering technology-based periodontal surgical procedures to increase gingival attachment during gingival augmentation.[42] Such techniques have allowed the growth of biopsy-derived gingival fibroblasts in tissue culture conditions within the hyaluronan-based biomaterial, followed by the application of the fibroblast-containing biomaterial into a surgical flap above the periosteum. The gingival tissue was subsequently observed to undergo sequential healing and improved gingival attachment, via the proposed mechanisms for hyaluronan in periodontal healing, including granulation tissue formation, HYAFF® degradation, re-epithelialization and angiogenesis, as described above.

Despite the apparent advantages of the application of exogenous hyaluronan in the healing and augmentation of non-mineralized periodontal tissues, it has been suggested that hyaluronan or hyaluronan-based biomaterials applied to the root surfaces of the tooth are unlikely to enhance the augmentation of mineralized periodontal tissues, as the root is avascular and therefore could not promote tissue regeneration.[42]

Nevertheless, another hyaluronan-based biomaterial, cross-linked hyaluronan, has recently been used as a carrier of the recombinant bone-regenerating extracellular matrix component, bone morphogenic protein-2 (BMP-2), during alveolar ridge augmentation.[43] The incorporation of BMP-2 into cross-linked hyaluronan has been clinically demonstrated to support significant high-density bone induction by BMP-2, although cross-linked hyaluronan exhibits no apparent osteoconductive potential itself. Furthermore, the cross-linked hyaluronan has been suggested to enhance bone regeneration by the protection of BMP-2 from enzymic degradation, by preventing periodontopathogen proliferation, by enhancing cell migration and proliferation at the bone defect and by promoting angiogenesis, via the mechanisms described above.[43]

As with gingival augmentation,[42] the hyaluronan-based biomaterial is degraded during the healing process.

CONCLUSION

Preliminary evidence suggests that hyaluronan may be a potential candidate as a mediator of non-mineralized periodontal tissue healing and as an aid to periodontal disease treatment. Hyaluronan achieves these effects by promoting a remission of symptoms, not only in the marginal gingivae, but also in the deeper-seated periodontal tissues, probably via the mechanisms established for hyaluronan in wound healing generally. Studies further imply that hyaluronan and hyaluronan-based biomaterials may be suitable carriers of cells from periodontal tissues or known tissue-regenerating extracellular matrix components in the augmentation of both mineralized and non-mineralized periodontal tissues.

Further laboratory-based research and large-scale randomized, controlled clinical trials into the therapeutic effects of hyaluronan and hyaluronan-based biomaterial application to periodontal sites are essential, if the true benefits of hyaluronan administration in periodontal healing and surgery are to be fully realized.

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ABSTRACT

BEHIND THE MASK
Surgical Face Masks in the Operating Theatre: Re-examining the Evidence. M.G. Romney *Journal of Hospital Infection* 2001; **47:** 251–256.

With the increased vigilance in cross-infection control over the last decade, we are now used routinely to donning a face mask for operative procedures. Surgical face masks were introduced by a German surgeon in 1897. Over recent years, the efficacy of face masks has been questioned. This review article examines some of the evidence behind the use of face masks for preventing operative infection and preventing transmission to the operator. On the subject of the former point, the review concluded that the evidence is at best equivocal and there is a paucity of randomized controlled trials. However, some studies have demonstrated that not wearing face masks did not increase the incidence of post-operative infection. The transmission of contaminated aerosols from patient to operator is more important in dentistry; again, there is little convincing evidence against this practice, although it has been argued that very small particles may still reach the operator's face directly through filter of the mask. The more recent introduction of full face visors has yet to be studied satisfactorily but may offer superior protection. For the time being, the evidence still advocates the use of the face mask for operative procedures.

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