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Hepatocyte Growth Factor And Periodontal Disease

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Abstract
Hepatocyte growth factor (HGF) is one of the various chemical factors that facilitate periodontal destruction. HGF affects nervous system, immune system and reticuloendothelial system. It is a protein secreted by mesenchymal cells such as fibroblasts, and promotes motility and matrix invasion of epithelial cells. HGF - a pluripotential regenerative cytokine - is a key factor in the pathogenesis and progression of periodontal disease, mostly through its over-stimulation of gingival epithelial cell growth and impairment of the regeneration of collagenous structures

Key Words
Hepatocyte Growth Factor, Scatter Factor, Gingival Crevicular Fluid, Periodontal Disease

Introduction:

Chronic periodontitis has been defined as an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment and bone loss[1]. Microbial products activate monocytes/macrophages to produce vasoactive substances such as prostaglandin E2, interferon, tumor necrosis factor etc. Out of the various chemical factors that facilitate periodontal destruction, is Hepatocyte growth factor (HGF).

Hepatocyte growth factor also known as scatter factor (SF) is a heteridimeric protein secrected by cells of the mesodermal origin. (HGF) affects nervous system, immune system and reticuloendothelial system. It induces a spectrum of biological activities in epithelial cells, inducing mitogenesis, stimulation of cell motility and the promotion of matrix invasion and is a potent angiogenic factor. HGF production is also induced by bacterial cell surface components. Hepatocyte growth factor (HGF) acts as a mitogen, motogen, morphogen, anti-apoptotic factor, and scatter factor for various kinds of epithelial cells. It is a protein secreted by mesenchymal cells such as fibroblasts, and promotes motility and matrix invasion of epithelial cells

Historical Background:

HGF was first described by stoker and perryman[2] as a secretory product of fibroblast which dissociates epithelial cells, thereby increasing their motility and invasiveness. HGF causes spread of the epithelial cells and hence also know as scatter factor. Weidner[3] further reveled that SF and HGF are identical.

Structure:

It is secreted as a single inactive polypeptide and is cleaved by serine proteases into a 69-kDa alpha-chain and 34-kDa beta-chain **(Fig.1)**. A disulfide bond between the alpha and beta chains produces the active, heterodimeric molecule. The protein belongs to the plasminogen subfamily of S1 peptidases but has no detectable protease activity. Alternative splicing of this gene produces multiple transcript variants encoding different isoform[4].

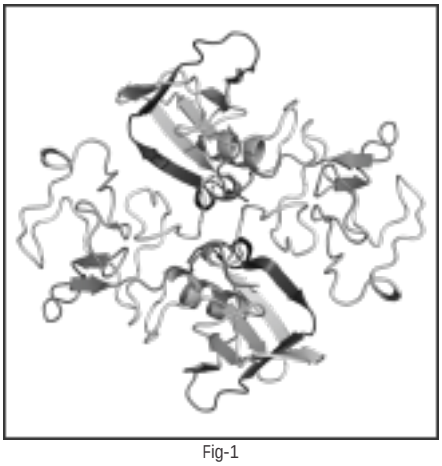

Fig-1

Sources:

Hgf is produced by mesenchymal cells such as fibroblasts, macrophages, smooth muscle cells, endothelial cells and the fat storing cells in the liver. The tissues that contain hgf protein are blood (monocytes, leukocytes and platelets), liver, lungs, brain, bone marrow, spleen and placenta.

HGF and Immune system:

Monocytes and macrophages:

Monocytes and macrophages posses CR1, CR3, CR4, C5Ar receptors and molecules important in antigen presentation (MHC class II receptor and Cd1). It has been shown that HGF is active on monocytes, induces migration and production of cytokines; furthermore monocyte activation enhances cell responsiveness to the factor by up-regulating the expression of the HGF receptor

Neutrophils: They are predominant

leukocytes in the blood. They possess many lysosomes within their cytoplasm. Because neutophils do not need to differentiate substantially to function, they are suited for rapid responses. The adherence of neutrophils to the endothelium depends on neutrophil integrins. HGF induces lymphocyte function-associated antigen (LFA)-1-mediated adhesion of neutrophils to endothelial cells. Furthermore HGF functionally transformed neutrophil integrin LFA-1 to active form and reduced surface L-selectin expression level.

Dendritic cells:

Dendritic cells (DC) are leukocytes with cytoplasmic projections or dendrites. They ingest antigen locally and transport the antigen to lymph nodes through afferent lymphatics. For DC to function, motility is an important property The HGF receptor c-MET is expressed in DC and is signaling competent, since it is effectively tyrosine phosphorylated in response to HGF. It has been demonstrated that HGF-activated c-MET regulates DC adhesion to the extracellular matrix component laminin. The antigen-presenting function is, however, unaffected.

T cells:

T cells recogonise diverse antigens using a low affinity transmembranous complex, Tcell antigen receptor. HGF was shown to induce both adhesion and migration of human T-cell subsets and can be detected immunohistochemically on inflamed endothelium. HGF preferentially induces responses from T cells of memory phenotype, in contrast to macrophage inflammatory protein 1ß (MIP-1ß), a chemokine which acts preferentially on naive cells.

HGF and Periodontal disease

Periodontal diseases are heterogeneous and include a variety of infections and inflammatory lesions. Notably, periodontitis is a prevalent disease that is characterized by loss of connective tissue attachment and alveolar bone around the teeth in conjunction with the formation of periodontal pockets due to apical migration of the junctional epithelium. The microbial nature of many periodontal diseases has been recognized long ago. More recently, it has been realized that the host related factors might be the keys to understanding of the disease processes in periodontitis. Periodontal disease progression is episodic in nature on a tooth site level; however, the risk of periodontal disease is principally patient based rather than site based.

Evidence has been emerging that hepatocyte growth factor (HGF) - a pluripotential regenerative cytokine - is a key factor in the pathogenesis and progression of periodontal disease, mostly through its over-stimulation of gingival epithelial cell growth and impairment of the regeneration of collagenous structures

To clarify whether HGF is involved in periodontal disease, the study was conducted by Ohshima M, Sakai A, Ito K, Otsuka K[5], to determine whether HGF is present in gingival crevicular fluid (GCF) and to investigate the relationship between levels of HGF and the clinical parameters of periodontal disease, probing depth (PD), gingival index (GI) and bleeding on probing (BOP). They examined and collected GCF samples from 80 sites in 38 subjects with periodontal or other oral diseases. The concentrations of HGF, IL-1beta and PGE2 were determined by ELISA, and active collagenase activity was determined by functional assay. The HGF level correlated positively with PD and GI, and was significantly higher in specimens from BOP-positive sites and those where PD exceeded 4 mm compared with those from sites that were BOP-negative or with a PD less than 3 mm. There was a significant positive correlation between the concentrations of HGF and IL-1beta. These results indicate that the HGF level in GCF correlates well with clinical parameters of periodontal disease, and suggest that HGF may be involved in epithelial invasion through its role as a scatter factor

Magdalena Wilczynska-Borawska et al[6] measured the levels of immunoreactive HGF in unstimulated whole mixed saliva from 26 patients referred for treatment of periodontal disease, and from 20 healthy subjects. HGF was detected in all saliva samples from the patients, the concentration ranging from 0.06 to 5.38 ng/ml, with a mean concentration of 1.87 ± 1.32 ng/ml. In healthy individuals, the median salivary HGF level was 0.68 ng/ml (range: 0 - 7.33 ng/ml), being almost 3-fold lower ($P < 0.0001$) than that in the patients. They found that the salivary HGF level was positively correlated with GI ($P = 0.004$), PBI ($P = 0.046$) and PI ($P = 0.001$), but not with PD ($P = 0.351$), CAL loss ($P = 0.172$), number of teeth ($P = 0.279$) or patient age ($P = 0.362$).Their findings suggested that salivary HGF concentration may be a novel marker of symptomatic periodontal disease, and that it warrants further validation.

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