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Preliminary Insights On Periostin As A Novel Biomarker For Collagen Metabolism Disorders And Periodontitis – An Overview

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ABSTRACT

Periodontitis is a complex, chronic inflammatory disease caused by pathogenic microflora that colonizes on the tooth surface evoking host immune responses which when left unchecked might result in tooth loss. Periostin is a matricellular protein that is highly expressed in the periosteum and periodontal ligament. It is an important protein involved in maintaining the integrity of the periodontal ligament and alveolar bone, hence its link in the etiopathogenesis of periodontal disease is much significant. Periostin is also expressed in various specialized tissues like heart valves, the connective tissue of lungs and kidneys where it helps in the formation of extracellular matrix. Since periostin acts as a scaffold for the formation of the extracellular matrix of various tissues and a remodeling protein in bone formation and metabolism, any disease affecting these structures would potentially influence the periostin levels. This review aims in eliciting the role of periostin in various metabolic disorders and emphasizes its role as a biomarker to scrutinize the disease progression.

Keywords: Periostin, bone, collagen metabolism, periodontitis

1. INTRODUCTION

The extracellular matrix consists of a dynamic organized structural network that forms an important part of any tissue microenvironment.[1] It plays a vital role in regulating tissue homeostasis where it interacts with the surrounding epithelial environment. [1] It also acts as a scaffold by providing various growth factors and proteins required for the process of wound healing and tissue repair. [1] There are various proteins expressed in the extracellular matrix which are a promising group of biocompatible materials that provides niches for cell adhesion, proliferation, differentiation, and apoptosis.[2] The matricellular proteins bind to various other extracellular matrix proteins, growth factors and cytokines where they interact with the specific receptors present on the cell membrane to remodel the tissue environment in diseased conditions.[2]These proteins are usually present in negligible levels in normal tissues but are highly expressed in the sites of injury and inflammation. [2] Research pieces of evidence on these proteins enumerate its potentiating role in inflammatory responses and tumor progression.

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Periostin, being one such non – structural extracellular matrix protein belonging to the member of the fasciclin I family with four repetitive fasciclin domains. [3] It is a secretive protein that was first identified in a mouse osteoblastic cell line as a cell adhesion protein in the year 1993 by Takeshita et al where he termed it as osteoblast specific factor (OSF – 2) and was recently classified as a novel matricellular protein. [3] This protein is specifically expressed in the periosteum, and periodontal ligament tissues, as well as in heart, lung, and tumor tissue. It is closely related to the formation, mineralization, and reconstruction of teeth and bone tissues.[4]Periostin has been reported as a critical player in regulating the inflammatory microenvironment in various diseases such as allergic disorders, atherosclerosis, fibrosis, cancer, bone metabolism and connective tissue disorders.[(5,6,7,8,9)]

Periodontitis is a complex long-standing multifactorial inflammatory disease affecting the soft and hard tissues surrounding the teeth.[10] As pathobiology of the disease is mediated by immune cells; it involves the release of certain cytokines, chemokines and proteins during various stages of disease progression which are useful in determining the accurate staging and grading of the disease as they are released during a précised time.[11] Periostin which is also known as periosteum protein affects the integrity of periodontal tissue structure and function and is closely related to the occurrence and development of periodontal disease, hence it can be considered as a sensitive diagnostic aid in the diagnosis and treatment of periodontitis.[12] Periostin protein exhibits a negative effect on reducing cell apoptosis in a hypoxic environment, thereby causing a positive significance in the treatment of periodontitis. [12]

This association between periostin and various systemic disorders promises its role as a diagnostic biomarker which is further explored in this article.

EXPRESSION OF PERIOSTIN IN NORMAL TISSUES

Periostin is superiorly expressed in the periosteum, which is a specialized membrane that covers the outer surface of bones thereby responsible for growth in bone diameter and the cortical thickness.[13] The activity of the periosteum is particularly upraised during the embryonic development phase and body growth, although during adult life, it contributes to determinate bone diameter and, subsequently, the strength of the bone. [14]The expression of periostin is well demonstrated in other connective tissues rich in collagen which is subjected to undergo mechanical stress. These structures include a specialized tissue of periodontium the periodontal ligament [15], heart valves[16], and tendons.[17]

PERIOSTIN IN INFLAMMATION

Inflammation is a host-generated immunological response to physical, chemical, mechanical or infectious stimuli which marks in minimizing the tissue damage and the spread of infectious stimuli. [18] The immune system plays a vital role in generating and modulating the inflammatory response which senses the tissue damage or pathogen-associated molecular patterns (PAMP) to restore the tissue hemostasis. [18] The underlying molecular mechanisms of the inflammatory

process unwind the fact that there are many chemokines and cytokines released by the inflammatory cells that exert effects on the extracellular matrix proteins thereby intervening in their function. [18] Periostin characterized as matricellular protein interacts with various surface integrin molecules that aids in wound healing, tissue repair and remodeling mechanism. [18] Its other mechanism of action during inflammation is that it triggers fibrosis by interacting with other extracellular proteins like osteopontin, tenascin C and fibronectin thereby exhibiting a stimulatory effect on fibroblasts proliferation and differentiation. [18] Thus periostin has been implicated as a key biomarker in regulating the inflammatory response in various systemic disorders which include atherosclerosis, pulmonary fibrosis, renal fibrosis, allergy disorders and periodontitis. [18]

PERIOSTIN AND SYSTEMIC DISORDERS

PERIOSTIN AND ATHEROSCLEROSIS

Atherosclerosis is defined as progressive narrowing and hardening of medium to large-sized coronary arteries due to the accumulation of plaque (fat, cholesterol crystals, calcium and other substances) in the layers of tunica intima and media which consists of the smooth muscle layer, collagen fibrils and elastic fibers. [19] It could potentiate serious conditions like coronary artery disease, peripheral arterial disease, myocardial infarction finally leading to thrombosis and stroke by the rupture of the thrombi. [19] Thus understanding the plausible biological mechanisms behind atherosclerotic plaque formation is therefore essential for developing novel therapeutic modalities to prevent or postpone the condition. Periostin levels are highly upregulated in atherosclerotic plaque samples when compared with normal heart valves. Extensive research over the last few decades has revealed that abnormalities in vascular smooth muscle cell (VSMC) activation, excess extracellular matrix (ECM) formation, chronic inflammation, and accumulation of cholesterol-rich debris are all linked to cardiovascular disease. The vascular smooth muscle cell upon abnormal activation shifts to a synthetic, proliferative phenotype in which they secrete proteins such as periostin, which leads to collagen formation. Periostin also stimulates the production of Matrix metalloproteinases (MMPs) which contribute to plaque instability by promoting the extracellular matrix breakdown leading to rupture of plaque, causing thromboembolism and stroke.[20]

PERIOSTIN AND ALLERGIC DISORDERS

Researchers have found that type II immunity is dominant in stimulating allergic inflammation. Thus the production of cytokines like IL-13, IL-4 produced by eosinophils, mast cells, basophils and helper T cells. Since periostin is a downstream product of IL-4/IL-13 its expression in the site of inflammation induces periostin expression. Thus periostin levels are upregulated in subepithelial sites of allergic disorders which include asthma, atopic dermatitis, allergic conjunctivitis and rhinosinusitis.[21]

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PERIOSTIN AND PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is a fatal interstitial lung disease that is characterized by progressive aberrant fibrosis of the lung matrix on the latter stages leading to respiratory failure. It predominantly affects the population of adults over 50 years of age and it has a worldwide incidence. The expression of periostin is exponentially increased in the lungs of idiopathic pulmonary fibrosis patients. Therefore, serum levels of periostin may predict clinical progression in this disease. Periostin increases myofibroblast proliferation and differentiation, thus leading to the synthesis of type 1 collagen, which contributes to abnormal lung fibrosis.[22]

PERIOSTIN AND CANCER

A developing tumor comprises a tissue microenvironment that is composed of proliferating tumor cells, the tumor stroma, blood vessels, infiltrating inflammatory cells and a variety of associated tissue. One of the microenvironment components which is more pronounced is multifaceted proteins grouped under the name of matricellular proteins. Periostin is one such matricellular protein that has been shown to regulate key aspects of tumor biology, including proliferation, invasion, matrix remodeling, and dissemination to pre-metastatic niches in a distant organ. In general, elevated periostin levels are usually associated with a more aggressive tumor behavior, advanced stage, or poor prognosis, suggesting that periostin levels could evolve as a prognostic biomarker.[23]

PERIOSTIN AND BONE METABOLISM DISORDERS

Periostin earlier referred to as osteoblast-specific factor was renamed due to its expression in bone especially in the periosteum which covers the outer surface of the bone and contributes to intramembranous bone embryogenesis and growth in diameter of bone. The presence of periostin protein was detected in mesenchymal cells and alkaline phosphatase expressing cells, that is, preosteoblasts and osteoblasts of the periosteum. Periostin is preferentially expressed in the periosteum at a high level during the phases of embryogenesis and bone growth. In adults, it is reexpressed after mechanical stress and fracture where bone formation is essential.In metastatic bone disease, periostin levels are increased with bone metastases. Thus, periostin may serve as an early indicator of bone metastases or periosteal apposition.[24]

2. ROLE OF PERIOSTIN IN PERIODONTIUM

COLLAGEN FIBRILLOGENESIS

The extracellular matrix of the periodontium is primarily composed of collagen. The PDL which is an anchoring fibril of the tooth to the bone is primarily composed of types I, V, VI collagen. Collagen is mainly required for the mechanical properties of the connective tissue and it provides tensile strength. Collagen fibrillogenesis is a complicated process that involves the synthesis of collagen in which many ECM proteins are involved. Several investigations have shown that

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periostin and collagen co-localize and have a molecular-level interaction in the periodontal ligament. The molecular mechanism behind the action of periostin in collagen cross-linking has been investigated, and the results have shown that periostin interacts with BMP-1 aiding in the formation of high stiffness collagen through effective collagen cross-linking.[25]

BONE FORMATION

Periostin plays a vital role in osteoblast adhesion, differentiation, and survival. It was reported to periostin plays a role in cell adhesion by the of support avb3 and avb5 integrins. The preferential expression of periostin in the periosteum, a major contributor to bone strength, suggests that it may be involved in bone microarchitecture. In teeth, the periodontal ligament is involved in the conveyance of forces to the bone resulting from mastication. This mechanical strain activates latent TGF-β1 (transforming growth factor- β1), a known prerequisite for up-regulation of certain pro-adhesive and matrix remodeling genes in fibroblasts that regulate periostin expression.[26]

Elevated levels of periostin are seen with a concomitant down-regulation in sclerostin, an antagonist of bone formation. The oral cavity is continuously subjected to mechanical stress conditions, this periostin protein helps in maintaining the bone integrity by stimulating osteoblast activity and suppressing the action of sclerostin by osteocytes, through integrin signaling.[26]

PERIOSTIN AND PERIODONTAL DISEASES

Periodontitis is a chronic infectious condition caused by gram-negative periodontal pathogenic bacteria which affects the structural integrity of periodontal tissues that include gingiva, cementum, alveolar bone and periodontal ligament thereby leading to periodontal pocket formation, clinical attachment loss and alveolar bone resorption resulting in tooth loss. Different molecules are released by the pathogenic bacteria as well as the host immune system in this scenario, which reflects in periodontal bone loss activity and susceptibility. Since there are a variety of molecules released during the pathogenesis of the disease, it is unlikely that a single biomarker for disease detection and prediction can be found. New insights into the pathogenesis of periodontitis disease depict that there is the incorporation of gene, protein and metabolite data into dynamic biological networks that is responsible for disease initiating and progression mechanism.[27]Periostin is one such modulator of critical matricellular interactions that is relevant in those processes. Periostin functions as a necessary protein for maintaining tissue integrity and maturation. Considering the elevated physiological levels of periostin in collagen-rich connective tissue, it is has been detected that increased gingival inflammation and periodontal destruction might result in the reduction in the periostin levels. Some studies highlighted that there exists a correlation between alveolar bone loss and level of periostin. In periodontitis patients, the decrease in the levels of periostin has been attributed to two reasons. The first reason being the bacteria, wherein bacterial competition might result in a reduction in periostin levels produced by PDL fibroblasts. The second reason being the reduction in the number of

PDL fibroblasts directly might result in a reduction in the level of periostin. Thus fall in the level of periostin diminishes PDL stability thereby increasing the risk of subsequent damage and inflammatory process due to reduction in the biomechanical and structural potential of PDL. Thus by considering the highly significant protective role of periostin in periodontal tissues, it can be employed as a reliable inflammatory biomarker for the detection of periodontal diseases. It can as well be used as a diagnostic biomarker for postoperative evaluation of the efficacy of interventions used in the treatment of periodontitis. Since GCF and saliva are rich in proteins, enzymes and pro-inflammatory cytokines, assessment of their components which includes periostin can reveal information about periodontal health. Thus, periostin can be employed as an effective diagnostic marker for the assessment of the health of periodontal tissue or the severity and progression of periodontal disease. Moreover, some studies quoted level of periostin decreases in the GCF following periodontal disease; therefore employing it as a reliable biomarker to determine the severity of the periodontal disease.[28]

PERIOSTIN AND PERIODONTAL REGENERATION

Regeneration and healing of the injured tissues in periodontal disease occur through the interactions between intracellular and extracellular matrix where complex molecules present in the matrix play an important role in this respect.[29] Therefore, the integrity of the extracellular matrix is a prerequisite to maintain the normal structure and function of tissues. The extracellular matrix locally releases molecules and proteins that work together as a complex network to physically protect the cells, tissues and organs.[29] In the past, researchers used to believe that the extracellular matrix only serves as a scaffold. In the present research studies, it is known as a fact that several cells and molecules are involved in cellular aspects such as cell morphology and differentiation by sending specific signals. The periodontal ligament that is connecting teeth to the underlying basal bone acts as a dynamic system to entrap the proteins and complex molecules of the extracellular matrix during the wound healing process.

Periostin has two main functions which include fibrillogenesis and bone formation. It helps in maintaining the integrity of the periodontal ligament by the formation of type I collagen. The occurrence of periostin is highly concentrated in collagen-rich tissues such as the heart, tendons and skin, PDL, the bone which issubjected to constant mechanical loads. The periostin expression has higher effects on neoangiogenesis and collagen formation which are two inevitable processes of wound healing and tissue repair.[30] Hence further research in this context would promise periostin as an excellent prognostic and regenerative marker to predict and cease the periodontal disease progression.

3. CONCLUSION

Periostin is a transient extracellular protein that helps in maintaining the structural integrity of various hard and soft tissues. It also plays a key role in stimulating the wound healing and tissue repair process. Owing to its coupling action, periostin has acquired a potential value as a disease

prognostic marker and as a promising regenerative material. The protein is also expressed in various biologically significant tissues at homeostatic levels. Its role in bringing about systemic inflammation in chronic disorders is not been clearly understood. Future researches on this aspect would throw insights into understanding the mechanism that could employ periostin protein as a disease-specific biomarker and tissue regenerative material in periodontitis and other systemic conditions.

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