

GLANCE INTO PROTEINS PRESENT IN PERIODONTAL TISSUES-A REVIEW – PART I

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Abstract

Proteins are the class of macromolecules containing nitrogen that are essential for the survival of life. Proteins are at the centre of biological processes and are essential structural components of the cells. Proteins execute a wide variety of specific and vital functions in the living cells. The periodontium is defined as “the tissues investing and supporting the teeth”. It consists of two soft tissues and two hard tissues. The supporting tissues of periodontium made up several molecules, cells and tissues embedded in different layers of matrix composition. Proteins present in periodontium involved in various functions such as cell matrix adhesion and signalling regulate diffusion of nutrients, waste products, and soluble signalling molecules. Periodontal disease is the major cause of tooth loss which occurs due to pathological changes in the supporting tissues. Abnormalities in either protein function or structure have been associated with various genetic and non-genetic diseases. Therefore the knowledge of different proteins present in periodontium is imperative to understand the physiology and pathology of the periodontal tissues. Hence this article reviews the list of various types of proteins present in gingiva and periodontal ligament of periodontium.

Key Words: - Periodontium, proteins, epithelium, connective tissue

Introduction

Proteins are the class of macromolecules containing nitrogen that are essential for the survival of life. Proteins are at the centre of biological processes and are essential structural components of the cells. The word protein is derived from a Greek word “proteios” which means “of the first rank” and the term was coined by Jons J Berzelius in 1838. Proteins execute a wide variety of specific and vital functions in living cells. These include proteins acting as enzymes, immunoglobulins, hormones, blood clotting factors, membrane receptors, storage proteins, muscle contraction, respiration etc.¹

The periodontium is defined as “the tissues investing and supporting the teeth”. It consists of two soft tissues and two hard tissues. The soft tissues are gingiva and periodontal ligament and hard tissues are cementum and alveolar bone. The various cells, tissues, and organs that compose the periodontium are complex entities that show unique developmental and functional characteristics.²

The supporting tissues of periodontium made up several molecules, cells and tissues embedded in different layers of matrix composition.³ Proteins present in periodontium involved in various functions such as cell matrix adhesion and signalling regulate diffusion of nutrients, waste products, and soluble signalling molecules; impart compressive strength and tensile to the tissues and in certain tissues provide the appropriate conditions for the nucleation and growth of mineral crystals.⁴

Periodontal disease is the major cause of tooth loss which occurs due to pathological changes in the supporting tissues. Abnormalities in either protein function or structure have been associated with various genetic and non-genetic diseases.⁵ Therefore the knowledge of different proteins present in periodontium is imperative to understand the

physiology and pathology of the periodontal tissues. Hence this article reviews the list of various types of proteins present in gingiva and periodontal ligament of periodontium.

PROTEINS PRESENT IN GINGIVA

Proteins in gingiva epithelium

The epithelium of gingiva is made up of stratified squamous cells and further subdivided into oral epithelium, sulcular epithelium and junctional epithelium.

Keratins are a diverse group of structural proteins that form the intermediate filament network responsible for maintaining the structural integrity of keratinocytes. There are around 30 families of keratin proteins divided into two groups namely acidic and basic which are arranged in pairs.

Keratins and certain keratin associated proteins are useful as markers of differentiation because their expression is both region and differentiation specific.⁶

The other proteins unrelated to keratins are produced during maturation process of the epithelium. The most extensively studied proteins are **keratolinin** and **involucrin** (envelop proteins) which are the chemically resistant structures located below the cell membrane.

Filaggrin is another protein present in gingival epithelium. The precursors of this protein are packed in keratohyaline granules. Filaggrin which is packed inside these granules appears during the sudden transition of horny layer and forms the matrix of the most differentiated epithelial cells.⁷

Proteins in basal lamina

The epithelium is joined to the underlying connective tissue by a basal lamina. The basal lamina has overall thickness of 50 to 100 nm lying approximately 100nm beneath the

epithelial basal layer. It consists of two structural components, the lamina lucida adjacent to the basal cell membrane and the lamina densa, between lamina lucida and the connective tissue. The protein associated with basal lamina is type IV collagen, an adhesive glycoprotein laminin and a heparan sulphate proteoglycan.⁸

Lamina fibroreticularis a third layer of epithelium constitutes an adhesive glycoprotein, fibronectin, type III collagen (reticular fibers), type VII collagen (anchoring fibrils) and other types of collagen. This layer helps to maintain the attachment of basal lamina to the underlying connective tissue.⁹

Proteins of gingival connective tissue

The connective tissue or the extracellular matrix (ECM) refers to the complex material surrounding the mammalian cells in tissues. The connective tissue matrix composed of various organic constituents and major protein components such as collagen, elastin, fibronectin and proteoglycans.

Collagen is the principal structural protein component of connective tissue matrix. It is rigid, rod-like molecule that resists stretching and maintains the integrity and tone of the periodontal connective tissues. The collagen super family constitutes 27 types of different types. The firmness is achieved by the gingival tissues that are composed of type I collagen. In addition to type I "collagen" type III is also seen in gingival connective tissue. Type III collagen is known as fetal collagen and is important in the early phases of wound healing and remains unmineralized. Collagen type VI is distributed with the elastin fibers along the blood vessels which imparts rigidity needed to maintain the elastic blood vessel wall from undergoing permanent deformation. The other collagen types associated with ECM are type II, V, X, XVIII which are dispersed along with type I collagen. The anchoring fibrils consisting of type VII collagen helps to reinforce epithelial attachment to the underlying tissue.¹⁰

Elastin is a rubber like protein secreted by fibroblasts and smooth muscle cells. Elastin aids the blood vessel to expand and to facilitate an increase in the volume of blood. Elastin is a negligible component of gingival connective tissue and accounts about 6% of the total tissue protein. Ultrastructurally, elastin fibers composed of two morphologic components: an amorphous elastin component constituting 90% of the mature fiber and a 10 to 12nm diameter microfibrillar component. For an elastic fiber to form, the glycoproteins and several microfibril associated glycoproteins are initially secreted and accumulated into microfibrils. The microfibrils then provide a scaffold for the deposition of elastin and assembly of elastic fibers. Immature elastic fibers consisting only of microfibrillar subunits are referred to as oxytalan fibers.¹¹

Fibronectin is a chief glycoprotein present in gingival connective tissue. It is produced by hepatocytes and fibroblasts and is considered as a principal protein of ECM as it binds the cells to the ECM essential for connective tissue turnover in the gingiva. Fibronectin is a large dimer

of two similar 230-270 Kd polypeptide subunits which are connected by disulfide bonds at the C-terminus. Through these associations, fibronectin is involved in the cell attachment, migration, differentiation, and growth.^{12,13}

Laminin is an essential component of attachment apparatus which facilitates epithelial attachment to the tooth. It is a large glycoprotein (900 kDa) containing 3 polypeptide chains linked by disulfide bonds to form an asymmetric cross-structure. It is produced by the epithelial cells and helps attachment to the type IV collagen of the lamina densa layer through nidogen. In embryonic tissues, laminin is the first extracellular protein noticed, and in mature tissues it is commonly found as the major non-collagen component in basement membranes. The laminins are involved in a variety of biological functions, including cell attachment, cell proliferation and cell differentiation.¹⁴

Proteoglycans

The proteoglycans are a large and diverse group of glycoproteins that are widely distributed in mammalian tissues. Proteoglycans are conjugated proteins containing glycosaminoglycans (GAGs) represented by numerous species, comprising chondroitin-4-sulfate, chondroitin-6-sulfate, heparan sulfate, heparin, hyaluronic acid and keratan sulfate. The important proteoglycans that are present in gingival connective tissue matrix are chondroitin sulfate and hyaluronic acid.¹⁵

Chondroitin sulfide is a proteoglycan that occupies a large solvent space in the interstitial spaces of the extracellular matrix. It is composed of disaccharide units of 'O' sulfated N-acetyl galactosamine and D-glucuronic acid. The sulphation may take place at the C-4 and C-6 of the N-acetyl galactosamine. Accordingly, the molecule is termed as chondroitin-4-sulfate, chondroitin-6-sulfate. Their concentration is greatest in mineralized tissues, for example cartilage and bone.¹⁶

Hyaluronic acid is a large glycosaminoglycan present in most connective tissues and is especially abundant in embryonic tissues and cartilage.¹⁷ The functions of hyaluronic acid are tissue hydration, cell-surface matrix interactions, tissue development, cell-migration, aggregation with aggrecan, CD44 and other components of matrix.¹⁸

PROTEINS OF PERIODONTAL LIGAMENT

The periodontal ligament is a highly specialized connective tissue located between the tooth and the alveolar bone. It contains complex vascular and highly cellular connective tissue. Most primary elements of the periodontal ligament are the principal fibers which are collagenous in nature that are arranged in bundles and several other non-collagenous proteins. Periodontal ligament contains huge amount of ground substance which fills the spaces between the fibers and cells.¹⁹

Proteins present in periodontal connective tissue

The extracellular matrix of periodontal ligament predominantly consists of collagen type I. Other than type I

collagen periodontal ligament also contains type III. A collagen subtype collagen XII which is a unique feature of periodontal ligament as it does not normally present in other soft tissues. Collagen XII is thought to be involved in three dimensional architecture of periodontal ligament fibers. Type XVIII collagen, which is a component of hemidesmosomes is also present in periodontal ligament along with the desmosomal complex of proteins.

Proteins present in periodontal ligament ground substance

The ground substance fills the spaces between the periodontal ligament fibers and cells. It consists of two main components glycosaminoglycans such as hyaluronic acid, heparan sulfate, dermatan sulfate, chondroitin sulfate and proteoglycans of which dermatan sulfate is the principle one, and glycoproteins such as fibronectin and laminin.

Glycosaminoglycans are long chains of repeated disaccharide units comprising of hexosamine and uronic acid. The function of glycosaminoglycans is to bind freely to various proteins and other molecules and their hydrophilic nature permits them to hold large amount of water.²⁰ Discussion of different glycosaminoglycans present in the periodontal ligament will follow.

Hyaluronic acid is a large glycosaminoglycan present commonly in connective tissues and is exclusively plentiful in embryonic tissues and cartilage. It has the biggest molecular size among all the glycosaminoglycans and binds to molecules such as CD44 through which it adheres to other matrix components. With its bound water, hyaluronic acid forms a viscous hydrated gel. In cartilage, hyaluronic acid forms a large aggregate with 50 to 100 molecules of the proteoglycan monomer aggrecan. Its central functions are to provide hydration to the matrix, support vascular development and it also plays a role in cell or matrix interactions.¹⁸

Chondroitin sulfide is a glycosaminoglycan compound that occupies a large solvent space in the interstitial spaces of the extracellular matrix,¹⁶ the details of which are already discussed in the previous section of the article.

Dermatan sulfate is similar to chondroitin sulfate except that the glucuronic acid is exchanged by L-iduronic acid. It is a disaccharide unit containing N-acetyl galactosamine and iduronic acid. Dermatan sulfate seems to be localized closely allied with collagen fibers and is predominantly marked at the epithelial connective tissue interface. It is commonly dispersed in mammalian tissues, but is more concentrated in soft tissues such as skin and tendon.²¹

Proteoglycans have been named so because of their chemical structure of a protein complex to a carbohydrate (glycan). The basic structure of a proteoglycan comprises of a core protein bound to one or more glycosaminoglycan chains. Versican and decorin are the two chief proteoglycans seen in the periodontal ligament.²²

Versican is a chondroitin sulfate proteoglycan that takes a large solvent space in the interstitial spaces of the connective tissue matrix. Versican, a primary proteoglycan of loose connective tissue, is a large macromolecule. The protein core consists of epidermal growth factor-like and lectin-like amino acid sequences. At the amino terminal is a hyaluronic acid-binding region and at the carboxy-terminal a complement regulatory protein-like domain. The protein core contains 14 attachment sites in the central region for glycosaminoglycans. This molecule has been thought to be secreted by fibroblasts.²³

Decorin is another proteoglycan present in the extracellular matrix, formerly known as PG-S2, dermatan sulfate PG-II and PG-40, this proteoglycan is approximately 120 kDa and contains only single glycosaminoglycan attachment site on the core protein. Based on its location in the body, the polysaccharide is either a dermatan sulfate or a chondroitin sulfate glycosaminoglycan. Inside the connective tissue, decorin has been recognized with collagen fibrils and fibronectin.²³

Fibromodulin and lumican are keratin sulfate rich proteoglycans which binds to collagen fibers present in the periodontal ligament. Fibromodulin and lumican are thought to be stated differently in inflammatory cells, macrophages and the endothelial cells in addition to the fibroblasts which are their chief source of expression.²⁴

Periostin is a lately identified protein which is evidenced to be present in periodontal ligament. It has been named so as it was found initially in periosteum. The biochemical structure of periostin is a disulfid linked protein that favors osteoblast attachment and spreading. It is critical for mediating epithelial-mesenchymal complex that is necessary for formation of periodontium. Periostin is assumed to play a role in response of periodontal ligament to mechanical stress. It is believed to be focused more in areas of pressure than in areas of tension. Hence periostin, therefore thought to be important for maintenance of periodontal ligament.²⁵

Glycoproteins are the protein molecules which are covalently bound to carbohydrates. Numerous glycoproteins are found in the ground substance; a number of these have adhesive properties. One of their main functions is to bind cells to extracellular matrix elements. The other functions of glycoproteins include their role as enzymes, hormones, transport proteins, structural proteins and receptors. Fibronectin, laminin, tenascin, thrombospondin are the glycoproteins present in the ground substance of periodontal ligament.²⁶

Fibronectin and laminin; their structure, synthesis and function is same as their role in gingival connective tissue and has been already discussed under the heading of proteins present in gingival connective tissue.¹⁴

Nidogen is a glycoprotein usually forms a stable noncovalent complex with the laminin. Nidogen acts as a bridge between laminin and collagen type IV. Laminin-nidogen complex is imperative for the maintenance of

integrity of the basement membrane. It interrelates with both cell surface proteins and extracellular matrix proteins. Nidogen appears to be controlled primarily by endothelial cells.²⁷

Vitronectin is a glycoprotein that is widely distributed in mesenchymal tissues. Vitronectin facilitates the assembling of innumerable matrix components. The supplementary functions of vitronectin include cell attachment, differentiation and conducive to osteoblast differentiation.²⁸

Tenascin is a large glycoprotein molecule with a six-arm, star-shaped structure. The tenascin molecule entails of 6 disulfide-linked polypeptide chains that spread from the center like the tentacles of an octopus. Tenascin binds to fibronectin and to proteoglycans, particularly the cell surface proteoglycan syndecan. Tenascin is synthesized at specific times and locations during embryogenesis and is present in adult connective tissues, but with a more restricted distribution. Even though the distribution of tenascin is restricted in adults, it is seen in elevated but transitory levels during the development of various tissues wound healing and oncogenesis.²⁹

Thrombospondin exists in a number of tissues and is synthesized by several cell types. Thrombospondin has a trimeric or pentameric structure. It demonstrates its functions at the cell surface and in the extracellular matrix to encourage cell attachment, spreading, and migration. Thrombospondin also is a key for the proper organization of collagen fibrils in the skin and cartilage.³⁰

Conclusion

Proteins may be defined as the high molecular weight polymers present in different body tissues including periodontium. Each periodontal component is distinct in its location, tissue architecture, biochemical and cellular composition. Patients with periodontal disease thought to produce morphological and functional changes in the molecular components including proteins of the periodontium. Hence the knowledge of different proteins present in periodontium is vital to understand the physiology and pathology of the periodontal tissues.

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