Review Article

Role of Fibroblast in Periodontal Heath and Disease: An Overview

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ABSTRACT

Fibroblasts are the principal cell type in the fibrous connective tissues of the periodontium. They perform important functions in development, physiology, defense, progression of disease as well as treatment of the different diseases of periodontium. The fibroblasts are the major resident cells which inhabitate the periodontal tissues. They are crucial for maintaining the connective tissues which support and anchor the tooth. Fibroblasts can synthesize and secrete a variety of extracellular molecules. There are mainly four types: collagens, elastins, proteoglycans and glycoproteins. The collagens altogether constitute the most abundant proteins found in our body. The ability of fibroblasts to proliferate, migrate, elongate, adhere, immobilize itself and commence matrix synthesis is critical for cell function, wound healing and tissue integrity. They also have an active role in host defense. By stimulation with bacterial pathogens and their products as well as with cytokines, gingival fibroblasts secrete various soluble mediators of inflammation. Little is known of their origins, synthesis of regulatory cytokines and growth factors in health and disease, and importance in soft tissue regeneration. Hence the aim of this review is to summarize the current literature regarding the concept of periodontal fibroblasts in health, disease and after periodontal therapy.

Keywords: Fibroblasts; cytokines, growth factors; periodontium

INTRODUCTION

The periodontium is a connective tissue organ, covered by epithelium that attaches the teeth to the bones of the jaws and provides the continually adapting apparatus for support of teeth during function. The periodontium comprises four connective tissues, two mineralized and two fibrous. The two mineralized tissues are cementum and alveolar bone; the two fibrous are: periodontal ligament and lamina propria of gingiva. Fibroblasts are the principal cell type in the fibrous connective tissues of the periodontium. They perform important functions in development, physiology, defence, progression of disease as well as treatment of the different diseases of periodontium.[1] Fibroblasts synthesize and remodel extracellular matrices including collagen and elastin fibres and a large complement of nonfibrillar glycoproteins. These cells also exhibit contractility and motility, functions that contribute to the structural organization of the tissue, especially during development of the periodontal ligament. As the fibroblast is the major cell type in the periodontal connective tissues, it plays a significant role in normal turnover, repair, and regeneration. In connective tissue remodeling, fibroblasts are capable of synthesis and phagocytosis of collagen and components of extracellular matrix and also produce cytokines with the capacity to mediate tissue destruction and to stimulate osteoclastic bone resorption. For example, matrix metalloproteinase - 1 is a fibroblast/macrophage derived enzyme with the ability to degrade extracellular matrix collagen at physiological pH and temperature.[2] Fibroblasts and other tissues of mesodermal origin are also capable of

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secreting tissue inhibitors of metalloproteinases. Collagenolytic inhibitors in periodontal tissues may have a regulatory role in modulating connective tissue degradation and are found in high concentrations at healthy periodontal sites. These examples underline the central role that fibroblasts play in remodeling of periodontal tissues including the PDL.

An emerging concept is that fibroblasts are not homogenous, but instead consist of subsets of cells which can regulate bone marrow derived cells such as lymphocytes. Though evidence indicates many different subtypes of fibroblasts, the principal function of these cells is to synthesize and maintain the components of the extracellular matrix of the connective tissue. This feature seems to be consistent for all types of fibroblasts, with variation in the types and amounts of matrix proteins synthesized occurring according to the tissue of origin, as well as localized functions of the cells within the tissues. These cells and their extracellular matrix products play pivotal roles in maintaining the structural integrity of connective tissues, in healing process, and in pathological alterations. Following injury to the tissues, wound healing requires the recruitment of cells with regenerative capacity to the site in order for tissue repair or regeneration to occur. The ability of fibroblasts to proliferate, migrate, elongate, adhere, immobilize itself and commence matrix synthesis is critical for cell function, wound healing and tissue integrity.[3] It is also possible that the periodontal ligament fibroblasts are motile contractile cells and that they are capable of generating a force for tooth eruption.[4] Therefore, the aim of this review is to summarize the current literature regarding the concept of periodontal fibroblasts in health, disease and after periodontal therapy.

METHODOLOY FOR SEARCH STRATEGY

A literature search Medline and PubMed databases were searched under the following key terms: “Fibroblasts,” “cytokines,” “gingiva,” “growth factors,” “periodontium,” and “fibroblast heterogenecity.” All keywords were restricted in title or abstract without the language limitation. Only highly relevant articles from manual and electronic databases were selected for the present review. The aim of this review is to highlight the current literature regarding the concept of periodontal fibroblasts in health, disease and after periodontal therapy.

LITERATURE REVIEW

Structure of the Fibroblast

Fibroblasts are normally recognized under the light microscope by their association with collagen fiber bundles. The resting fibroblast (e.g. in tendons) has flattened, darkstaining, closed nucleus and little cytoplasm. The active fibroblast (e.g. in PDL) has pale staining open-faced nucleus and much more cytoplasm. The active fibroblasts are seen to have the usual complement of cytoplasmic organelles, but in exaggerated amounts so that there are a number of golgi complexes and many profiles of rough endoplasmic reticulum, mitochondria and secretory vesicles. These all are indicative of these cells’ synthetic and secretory function.[5]

Cytoskeleton: Fibroblast possesses a cytoskeleton demonstrable with special staining techniques that consist of microtubules and filaments. Microtubules are long gently curving cylindrical protein structures with an average diameter of 240 nm. The major protein making up the tubule is called tubulin and very similar to the muscle protein actin. The function of microtubules is associated with maintaining the shape of the cell and the position of its intracellular structures as well as determining secretory pathways. Filaments are of two types distinguished on the basis of their diameter-microfilaments (less than 80nm diameter) and intermediate filaments (80 to 120nm). Microfilaments composed of the contractile proteins actin and myosin which serve as intracellular muscles.[5] They are concerned with the maintenance of cell shape and with cytoplasmic movement and cell motility.

Contraction and Motility: The cytoskeleton of the fibroblast, containing contractile proteins, enables the fibroblast to contract. This ability to contract is expressed in a number of ways, but in particular, it manifests itself as an ability of the cell to move. A fibroblast grown in a culture dish “crawls” about by extending a leading edge, attaching that edge to the substratum by means of

an attachment plaque and then contracting and pulling itself forward as a sailor climbing a rope. The fibroblast can also influence its immediate environment if it remains stationary and utilizes its contractile properties to pull on adjacent structural elements just as a sailor hauling in a sail. An intermediate situation exists that involves both fibroblast movement and the influence of this movement on the immediate environment. Fibroblasts crawling about on collagen gel cause the gel to wrinkle.[5]

Junctions: When fibroblasts come into contact with each other (which is not the normal circumstance but does occur in PDL), their plasma membranes develop junctional arrangements. Junctional arrangements between cells are usually described in the context of contacts between epithelial cells (where they are more frequent, given the functions of epithelium to protect and seal).[5]

Three types of junctions are described: (1) tight or occluding (2) adhering and (3) gap. Further descriptive breakdown of junctions is made on the basis of their extent and shape. Thus, if a junction encircles or girdles the cell, it is prefixed by the term zonula (e.g. zonula adherence or zonula occludens) and if it is more circumscribed, the prefix macula is used (macula occludens). In tight junction the fusion of adjacent cell membranes occurs much as the teeth of a zipper intermesh and generally such junctions prevent any movement of material between cells.[5] In occluding or tight junctions, the opposing cell membranes are held in close contact by the presence of transmembrane adhesive proteins arranged in anastomosing strands that encircle the cell. The intercellular space essentially is obliterated at the tight junction. The transmembrane adhesive proteins which include occludin, members of the claudin family and in some tissues junctional adhesion molecule interact homotypically with the same proteins on the adjacent cell. Several cytoplasmic proteins associate with the intracellular portions of the transmembrane proteins; these include cell polarity–related proteins, vesicular transport–related proteins, kinases, transcription factors, and a tumor suppressor protein. In addition, some of the cytoplasmic proteins of the tight junctions bind to actin filaments. Tight junctions control the passage of material through the intercellular spaces (e.g., from the interstitium to the lumen of a gland). They also have an important role as a "fence" to define and maintain the two major domains of the cell membrane, the apical and basolateral surfaces.[6]

Cell-matrix junctions have a structural organization similar to that of cell-cell adhesive junctions, but they use different molecular components and attach the cell to the extracellular matrix. In focal adhesions the transmembrane component is a member of the integrin family of adhesion molecules. Integrins are heterodimers of different alpha and beta subunits that occur in different combinations with specificity for various extracellular matrix molecules. Junctions of the adherens type may be zonular or macular in form. In the zonula adherens a gap of some 20 nm is maintained between the opposing cell membrane that is filled with filamentous material. Microfilaments anchor themselves to the cytoplasmic face of this junction. In the macula adherens, also commonly known as the desmosome, a gap is maintained between the cells of some 30 nm who center is occupied by a dark line (thought to represent a region where transmembrane linkers fuse). The adjacent cell membranes are somewhat thickened and again internal filaments anchor themselves to the cytoplasmic portion of the membrane. Another form of the macula adherens is the hemidesmosomes, which is found on the surface of epithelial cells in contact with noncellullar surfaces such as the basal lamina or enamel in the case of the dentogingival junction.[5]

Hemidesmosomes link the cell to the basal lamina and, through additional extracellular molecules, to the rest of the extracellular matrix. The transmembrane adhesive molecules present in hemidesmosomes are the integrin α6β4, which binds specifically to the basal lamina glycoprotein laminin, and collagen XVII (also identified as BP180).[6] A gap junction is spot like in outline and a region where the two opposing cell membranes come close together but maintain a gap of about 3nm. Across this gap run numerous tubular structures with lumina some 2 nm in diameter that directly link the interiors of contiguous cells. Ions and small water-soluble molecules pass unimpeded through these gaps.[5]

Small molecules, such as ions and signaling molecules can move readily from one cell to another. Gap junctions electrically couple cells and allow for a coordinated response to a stimulus by the cells that are interconnected. Fibroblasts exhibit junctions of both the gap and the adherens type. Fibroblasts have the ability to adhere to their external environment through a series of transmembrane molecules (integrins, syndecan, CD44) that have an intercellular domain binding to cytoskeletal elements, a transmembrane domain, and an extracellular domain that binds to any number of extracellular matrix components. Such transmembrane molecules may also serve as membrane receptors. Morphologically this coupling arrangement has been described as a fibronexus.[5]

SECRETORY PRODUCTS OF FIBROBLASTS

Fibroblasts can synthesize and secrete a variety of extracellular molecules. There are mainly four types: (1) collagens (2) elastins (3) proteoglycans and (4) glycoproteins.

Collagens: The collagen superfamily contains at least 27 types of collagens that together constitute the most abundant proteins found in the body. All collagens are composed of three polypeptide alpha chains coiled around each other to form the typical collagen triple-helix configuration. Common features include the presence of the amino acid glycine in every third position (Gly-X-Y repeating sequence), of hydroxyproline and hydroxylysine and of noncollagenous domains and a high proportion of proline residues. Variations among the collagens include differences in the assembly of the basic polypeptide chains, lengths of the triple helix, interruptions in the helix, and the terminations of the helical domains.[6] Mesenchymal cells and their derivatives (fibroblasts, chondrocytes, osteoblasts, odontoblasts, and cementoblasts) are the major producers of collagens. Other cell types (such as epithelial, endothelial, muscle and Schwann cells) also synthesize collagens, although on a more limited basis in terms of amount and variety of collagen types.[6]

The collagen superfamily is subdivided into nine subfamilies largely based on their supramolecular assemblies:

1. Fibrillar collagens (types I, II, III, V, XI, XXIV, and XXVII)
2. Basal lamina collagen (type IV)
3. Fibril-associated collagens with interrupted triple helices (FACIT): Collagens IX, XII, XIV, XVI, XIX, XX, XXI and XXII consist of chains that have different lengths and contain a variety of noncollagenous domains. They exhibit several interruptions in the triple helix and are found in various locations in different tissues.
4. Network-forming collagens: Type VIII collagen assembles into a hexagonal lattice, which is believed to impart compressive strength while providing an open, porous meshwork. Type X collagen has a similar size and structure and is largely restricted to the hypertrophic zone of the epiphyseal cartilage growth plate.
5. Anchoring-fibril collagen: Collagen VII has unusually large non-helical ends making up two thirds of the size of the molecule.
6. Microfibril-forming collagen: Type VI collagen, which has large N- and C-terminal globular domains that associate in an end-to-end fashion, forms beaded filaments.
7. Transmembrane collagen types XIII, XVII, XXIII, and XXV.
8. Multiplexin (endostatin-forming) collagens: Type XVIII collagen is a component of basal laminae of epithelial and endothelial cells and is believed to stabilize structures of the basal lamina. Type XVIII collagen has multiple interruptions in the central helical domain and a large, unique C-terminal non-helical domain.
9. Other collagens: There are other collagens and proteins containing helical collagenous domains that cannot be classified into other category. Type XXVI is found in the extracellular matrix of the testis and ovary; however, its function and association with other collagens or matrix proteins have not been established. Type XXVIII is predominantly expressed in the basement membranes around Schwann cells of the peripheral nervous system and dorsal root ganglia. There is also a highly heterogeneous group of proteins that contain helical

collagenous domains but have not been clearly defined as collagens.[6]

Inherited Diseases Involving Collagens

Several mutations occur in collagen genes, resulting in a variety of different phenotypes depending on the affected collagen. Some of the more common mutations include osteogenesis imperfecta, or brittle bone disease, caused by mutations of the type I collagen genes and often including dental abnormalities; several types of Ehlers-Danlos syndrome (hyperextensible skin, hypermobile joints, and tissue fragility), resulting from mutations in the type I, type III, or type V collagen genes; Stickler's syndrome, caused by mutations in the type II or type XI collagen genes and characterized by retinal detachments, cataracts, hearing loss, joint problems, cleft palate, and facial and dental abnormalities; Alport's syndrome, nephrosis caused by defects of the basal lamina in the kidney glomerulus and sensorineural hearing loss because of mutations in certain type IV collagen genes; and different forms of epidermolysis bullosa, a separation of the epidermis and dermis, caused by mutations of the type VII or type XVII collagen genes.[6]

Gingival Fibroblast & Periodontal Ligament Fibroblast

Gingival fibroblasts (GF) are the most abundant cell type in periodontal connective tissues. Periodontal ligament fibroblasts (PDLF) and GF have distinct functional activities in the regeneration and repair of periodontal tissues as well as in inflammatory periodontal diseases.[7] Berahim *et al*.[8] performed a pilot study in vitro gingival fibroblast differentiation in a spheroid culture. They concluded that GF can be grown consistently in spheroid form but the cells appeared to differentiate along a chondrogenic lineage rather than a fibrous connective tissue lineage. Gingival fibroblasts, the major cell type in periodontal connective tissues, provide a tissue framework for tooth anchorage. Recently, they were presumed to be immunologically inert. Researchers recognized their active role in host defense. Upon stimulation with bacterial pathogens and their products as well as with cytokines, gingival fibroblasts secrete various soluble mediators of inflammation such as IFN-γ, PGE2, IL-1, IL-6, and IL-8 and up-regulate expression of HLA-DR and ICAM-1. These fibroblast-derived mediators and surface antigens are thought to play an important role in periodontal inflammatory response. Recently, human gingival fibroblasts (HGFs) have been demonstrated to express TLRs 2, 4, and 9. TLRs are recognized as key pathogen recognition receptors that sense microbial invasion.[9] TLR ligation triggers inflammatory innate immune response, which is critical for pathogen elimination. It is likely that the release of inflammatory mediators from HGFs in response to microbial stimuli occurs via TLR triggering. Recent findings also suggest that fibroblasts play an important role in negative feedback inhibition of inflammatory T cell response.[9]

Fibroblast Growth Factors: FGF was discovered in 1974 as a protein in cow pituitary glands that strongly induced proliferation of fibroblasts. In 1984, two proteins with different basic and acidic isoelectric points were identified as acidic FGF (aFGF, FGF-1) and basic FGF (bFGF, FGF-2).[10] The proteins have been classified into seven subfamilies: FGF-1 (FGF-1/2), FGF-4 (FGF- 4/5/6), FGF-7 (FGF-3/7/10/22), FGF-8 (FGF-8/17/18), FGF-9 (FGF-9/16/20), FGF - 11 (F G F - 11/12/13/14) and FGF-19 (FGF-19/21/23) based on structural similarities with each subfamily consisting of two to four types of FGF. Nearly all FGFs transmit signals via receptor-type tyrosine kinase. When FGF binds to a receptor tyrosine kinase is activated. Following activation, various tyrosine residues on the receptor are phosphorylated and signal transmission is triggered by the binding of effector proteins to these sites (Table: 1).[10]

Table 1: List of Factors Produced by Fibroblasts[10]

1.	FGF2	Fibroblast growth factor 2
2.	HGF	Hepatocyte growth factor
3.	IGF1	Isulin-like growth factor-1
4.	IL1	Interleukin-1
5.	IL6	Interleukin-6
6.	IL8	Interleukin-8
7.	KGF	Keratinocyte growth factor
8.	PGE2	ProstaglandinE2
9.	PDGF	Platelet-derived growth factor
10.	TGF β	Transforming growth factor β
11.	TNF α	Tumor necrosis factor α
12.	VEGF	Vascular endothelial growth factor

Medical uses of FGF-2: FGF-2 facilitates reactions that are necessary for revascularization, migration and proliferation of endothelial cells and regenerates capillary blood vessels in the healing of intractable ulcers.[10] Fibroblasts not only produce collagen but also develop into myofibroblasts and induce so-called wound constriction. It has been reported that when anti–FGF-2 antibodies are administered to normal animals that show normal wound healing both granulation and wound healing are inhibited.[11] FGF-2 facilitates fracture healing by promoting the proliferation of marrow-derived mesenchymal cells and inducing their differentiation into osteoblasts. It is thought that FGF-2 promotes the healing of fractures by stimulating both the growth and biochemical functions of mesenchymal stem cells.[12] Pitaru *et al.* found that after FGF-2 stimulation cell proliferation occurred and increased amounts of hydroxyproline and proteins were present in the initial stage. This was followed by alkaline phosphatase (ALP) activity and increased osteocalcin and calcification in later stages of healing of fractures.[13] FGF-2 has a powerful angiogenic action and clinical trials are being performed on intermittent claudication in peripheral arterial disease and atherosclerotic peripheral vascular disease. Clinical studies are also being performed on peripheral occlusive arterial disease with FGF-2 gene transfer and the powerful angiogenesis action of FGF-2 is thought to be one of the most promising treatment factors in therapeutic angiogenesis.[10]

FGF-2 in Periodontal Bio-regeneration: FGF-2 promotes proliferation of fibroblasts and osteoblasts and enhances angiogenesis. These activities are directly associated with periodontal tissue regeneration. However, periodontal ligament cells are the key players during periodontal tissue regeneration. To expose the molecular and cellular mechanisms by which FGF-2 induces periodontal tissue regeneration and various vitro experiments were conducted in which the effects of FGF-2 on periodontal ligament cells were examined. Experiments showed that periodontal ligament cells express FGFR1 and FGFR2 mRNA. In contrast, gingival epithelial cells express mRNA of FGFR1, 2, 3, and 4.[14] The responsiveness to FGF-2 is higher in undifferentiated periodontal ligament cells than in mature periodontal ligament cells.[10]

Future outlook for FGF-2 therapy: Numerous studies have been performed in order to examine the safety, effectiveness, and mechanism of FGF-2–induced periodontal tissue regeneration. For ideal tissue regeneration it is very important to fully apply the concept of "tissue engineering." Topical application of FGF-2 significantly induces periodontal tissue regeneration including osteogenesis and cementogenesis in animal models. It is also remarkable that no gingival epithelial downgrowth was observed at FGF-2–treated sites without barriermembranes. This suggests that FGF-2 is useful for periodontal regeneration of intraosseous bone defects.[10] However, in order to treat severe bony defects or horizontal bone resorption with FGF-2, it is essential to introduce the concept of a "scaffold" into the FGF-2 carrier. FGF-2 carrier provides a moldable and osteoconductive scaffold for undifferentiated cell types would dramatically increase its applications. Topical application of FGF-2 may be helpful in inducing bone augmentation or promoting Osseointegration of implants. Studies to investigate its efficacy are now in progress.[10]

Subpopulations of Gingival Fibroblasts: Bordin and Page in 1984[15] using an anti C1q antibody (Complement Component) and FACS (Fluorescence Activated Cell Sorting) separation derived two subpopulations:-

a. One cell fraction expressed C1q receptor which could bind the C1q globular head domain. It has the capacity to induce non-immune activation of classical complement cascade.
b. One cell fraction expressed low affinity for C1 q receptor which could bind the C1q collagen like domain. It plays a role in adhesion of fibroblasts to matrix component.

In health, periodontal ligament fibroblasts are larger than gingival fibroblasts, exhibit more filamentous actin and display smooth-muscle myosin. Alkaline phosphatase is found at much higher levels in periodontal ligament fibroblasts which also respond to cemental-derived mitogens differently than do gingival fibroblasts. Within these fibroblast populations, there is variation in

cell shape, proliferative capacity, and collagen synthesis. Thus, the periodontium may maintain homeostasis by creation of cellular diversity (Table: 2).[16]

Table 2: Fibroblast in Health and Disease[16]

Healthy fibroblasts	Diseased fibroblasts
Smaller in size	Bigger in size
Cell shapes found spindle; epitheliod; stellate	Only stellate cells found Low proliferation rate and reduced cloning efficiency
Greater proliferation rate and higher cloning efficiency	EGF receptors present Secrete small-molecular mass hyaluronic acid
No Epidermal Growth Factor (EGF) receptors	Increase in m-RNA for Type I collagen production

Fibroblast Heterogeneity:

In *vivo*, fibroblasts exhibit a range of morphological and functional characteristics including a cigar-shaped or stellate morphology in vitro but a highly variable set of morphologies in *vivo*. These cells have the ability to synthesize various extracellular proteins such as collagen and fibronectin but can also undertake other functions (e.g. as immune accessory cells) which extend their utility as "architects and caretakers of connective tissues."[17] Thus, it is possible to describe heterogeneous behavior in gingival or periodontal ligament cell populations that are in fact the result of a description of totally different cell types. For example, tissue macrophages and fibroblasts are morphologically very similar at the light microscope level.[18]In spite of their similar appearance to one another cultured populations of "pure" fibroblasts are highly diverse populations of cells that exhibit a considerable degree of heterogeneity.[19] Inter-site heterogeneity including variations in proliferative potential, alkaline phosphatase activity, response to growth factors, collagenase biosynthesis and cytoskeletal proteins is well-documented in cultured cells. [20-24] In periodontal tissues, the presence of subpopulations with various metabolic capacities and responses to environmental signals indicates that fibroblast heterogeneity has a significant impact on several clinically relevant issues in periodontology. Potential effect of fibroblast subpopulations in periodontology are:[20]

- Generation and maintenance of tissue form
- Pathogenesis of periodontal pocket formation
- Formation of fibrotic lesions in gingiva
- Differential cell repopulation by tissue barriers in wound healing
- Orthodontic tooth movement and treatment relapse[20]

Fibroblasts in immune function

Chronic inflammatory reactions are usually characterized by inflammatory cell accumulation in the extravascular connective tissue. In such sites, inappropriate activation of circulating or resident lymphocytes becomes self-perpetuating and can lead to chronic tissue destruction. In addition to that, the locally infiltrated lymphocytes should have an opportunity to interact directly with fibroblasts composing the connective tissue. The direct interactions of those different cell types seem to play important roles in lymphocyte lodging and retention in such sites. In fact, it has been demonstrated that lymphocytes interact with various non-hematopoietic cells, such as epithelial cells and endothelial cells. Regarding interactions with fibroblasts, it has been shown that IFNγ-stimulated fibroblasts can regulate the proliferative responses of T-lymphocytes both positively and negatively. Furthermore, activated lymphocytes have demonstrated strong binding ability to various fibroblast cell lines. Blocking experiments utilizing monoclonal antibodies specific to various cell adhesion molecules revealed that very late antigen (VLA) integrins, lymphocyte-function-associated antigen (LFA-1)/intercellular adhesion molecule-I (ICAM-1), CD44/ hyarulonate are, at least in part, involved in lymphocyte-fibroblast interactions.[25]

Turnover and Remodeling: Turnover and remodeling in the periodontal ligament imply synthesis and breakdown of matrix components, particularly the collagenous fiber meshwork that extends between cementum and bone. It has been suggested that remodeling of the ligament is confined largely to the mid-region of the periodontal ligament where fibers from the bone and fibers from the tooth interdigitate in an “intermediate plexus.” Turnover and remodeling

activity in teeth of limited eruption, like the molars of rodents, are found throughout the width of the periodontal ligament from cementum to bone. To adapt to changes of tooth position, the fiber systems in the periodontal ligament must be degraded and new fibers synthesized. Since the periodontal ligament is not made up of single strands of straight collagen fibers but consists instead of a complex meshwork, remodeling does not necessarily occur at all sites synchronously. There is apparently some flexibility in the system to permit adaptational changes by breaking down short stretches of collagen fiber bundles or single fibrils while leaving others intact. This highly localized remodeling process is undoubtedly facilitated by the phagocytosis of collagen. Unlike the bulk removal of collagen that is effected by extracellular matrix metalloproteinases, collagen phagocytosis enables periodontal ligament fibroblasts to very precisely remove collagen fibrils at specific sites.[26]

Growth factor-mediated control of Fibroblast function during Oral Wound Healing

Immediately after wound formation activated platelets and other immunocytes as well as resident cells secrete a large number of growth factors (e.g. platelet-derived growth factor, transforming growth factor beta, insulin-like growth factors I and II, basic fibroblast growth factor and epidermal growth factor) into the wounded area. These

factors regulate important functions such as the migration, proliferation and contraction of several cell types, of which the most important in granulation tissues are fibroblasts.[27] Migration of fibroblasts into the injured area represents an immediate tissue response to injury, as these cells can populate this region and secrete the extracellular matrix components required for healing. Many of the growth factors (platelet-derived growth factor, transforming growth factor β, insulin-like growth factor and epidermal growth factor) can stimulate the migration of human gingival fibroblasts in a dose-dependent manner.[28] Platelet-derived growth factor shown its migratory action mediated through the p38 mitogen-activated protein kinase signal-transduction pathway. In addition, platelet derived growth factor stimulates the migration of gingival fibroblasts on titanium surfaces

which has been correlated with the release of urokinase-type plasminogen activator. In-vitro studies shown that gingival fibroblasts are stimulated to proliferate by platelet derived growth factor, insulin-like growth factor I, epidermal growth factor and basic fibroblast growth factor. On the other hand, transforming growth factor-beta is a pleiotropic factor whose mitogenic action depends on the target cell type and developmental origin of fibroblasts. However, others have shown that transforming growth factor- β1 stimulates the proliferation of gingival fibroblasts. Platelet-rich plasma containing all the factors (platelet-derived growth factor, transforming growth factor beta, insulin-like growth factors I and II, basic fibroblast growth factor and epidermal growth factor) also stimulates gingival fibroblast proliferation. In the later stages of wound healing, the newly formed provisional extracellular matrix is replaced with granulation tissue. Myofibroblasts play a critical role in tissue contraction because of their ability to exert contractile forces.[29] Several growth factors known to speed the healing process such as platelet-derived growth factor, transforming growth factor-beta and insulin-like growth factors, have been shown to enhance the contraction of three-dimensional collagen matrices populated by human gingival fibroblasts.[30]

Functions of the Fibroblasts

a. Synthesis and deposition of the extracellular matrix
b. Tissue turnover and remodeling during various physiological and pathological processes.
c. Tissue integrity and homeostasis.
d. Wound healing- fibroblasts can become contractile and participate in wound contraction, in which case they develop intra cytoplasmic actin filaments.
e. Chemotaxis and phagocytosing foreign objects and ingesting cross-linked collagen; regulating local inflammatory responses.
f. Modulating behavior of neighbouring tissues and cells i.e., cell-cell interactions with epithelium and lymphocytes.

g. Periodontal Regeneration.

CONCLUSION

The principal cell in the lamina propria of oral mucosa and the periodontal ligament is the fibroblast, which is responsible for the elaboration and the turnover of fibres and ground substance. The fibroblast thus plays a key role in maintaining tissue integrity. Fibroblasts contribute to periodontal homeostasis by their abilities to remodel tissues, to repopulate wounds, to influence the metabolism of other cell types and to create a new fibrous attachment. Progenitor cell populations of the PDL are enriched in locations adjacent to blood vessels and in contiguous endosteal spaces. In normally functioning periodontal tissues, there is a relatively modest turnover of cells in which apoptotic cell death balances proliferation. Large increases of cell formation and cell differentiation occur after application of orthodontic forces or wounding. As PDL cells comprise multiple cellular phenotypes, it has been postulated that after wounding, the separate phenotypes repopulating the site will ultimately dictate the tissue form and type. PDL fibroblasts play an essential role in responses to mechanical force loading of the tooth by remodeling and repairing damaged matrix components. In consideration of the important roles played by fibroblasts in periodontal tissue homeostasis, they could be described as "the architect, builder, and caretaker" of the periodontal tissues.

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