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Review Article

Extracellular matrix: A regenerative conduit in dentistry

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ABSTRACT

Periodontal disease causes tooth loss by destroying the attachment system and tooth supporting tissues. Periodontal therapy seeks to not only halt the advancement of periodontal disease, but also to repair lost structures caused by disease progression. Extracellular matrix (ECM) is a complex three-dimensional network made up of an array of multidomain macromolecules organised in a cell/tissue-specific manner that serves as a structural scaffold in the formation of supramolecular assemblies in tissue architecture that regulate cell growth and differentiation, thereby providing a suitable biochemical and biomechanical microenvironment for regeneration of lost tissue structures. This article's goal is to provide a simplified and concise understanding of the structure and components of ECM, as well as to shed light on its utility as a regenerative conduit in the field of periodontal regeneration.

1. Introduction

The periodontium is a highly hierarchical organ composed of intercalated soft (gingival and periodontal ligament) and hard (cementum and alveolar bone) tissues that mechanically support the teeth and play an important role in transferring mechanical stresses during mastication.[1]

Periodontal disease is a multifactorial, inflammatory illness of the periodontal tissues characterized by loss of connective tissue attachment and degradation of periodontal ligament fibers and the surrounding bone.[2]

Periodontal therapy aims to eradicate the inflammatory process, limit the advancement of periodontal disease, and regenerate the tooth's supporting tissues, which include alveolar bone, periodontal ligament, and cementum over a previously damaged root surface.[3]

Recently, the realization has dawned upon clinicians that by combining transplanted biomaterials containing appropriately selected and primed cells, with mix of growth factors, signaling molecules and extracellular matrix (ECM) components, the host cell expansion and specialization can be facilitated in order to achieve periodontal regeneration, a process termed as tissue engineering.[4] (Figure 1)

All tissues and organs contain a mixture of cellular and non-cellular components, which form well organized networks called extracellular matrix (ECM). The ECM not only serves as physical scaffolding into which cells are implanted, but it also serves as a communication conduit between cells in organs and tissues by coordinating various signaling inside-out or outside-in directives.. As a result, ECM regulates cellular physiology, growth, survival, differentiation, and adhesion to control tissue morphogenesis, development, and homeostasis.[5] (Figure 2)

The major constituents of ECM are collagens (28 members divided into several subfamilies) and non-collagen proteins which comprises of proteoglycans, glycoproteins and elastin. Proteoglycans consists of protein core (decorin and biglycan) with glycosaminoglycan side chain attached

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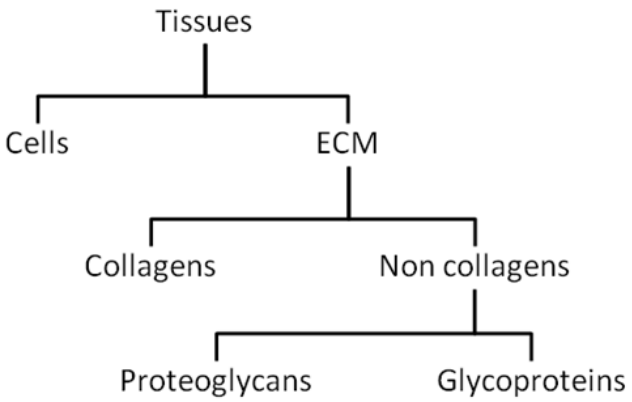
to it. Glycoproteins comprises of laminin and fibronectin that serve as cell adhesion proteins.(Figure 3) These multi-molecular structures utilizes one another to create a complicated 3D matrix network.[6]



2. Components of ECM

2.1. Collagen

Polymeric fibers are used to construct the majority of biological tissues. Cellulose and collagen are among the most numerous fibers found in nature. Cellulose, a significant component of plant cell walls, gives the plant body stiffness, while collagen is a key component of mammalian bodies and is abundant in tendon, bone, skin, cornea, and cartilage, and so on. Collagen is the most prevalent ECM protein, accounting for up to 30% of total proteins; it is largely synthesized and produced by fibroblasts in the ECM. They support the tissue by providing mechanical strength, stability, and elasticity.[7]

All tissues contain a mixture of several collagen types and demonstrate considerable variability in their proportion.The collagen family has 28 members, each with a unique supramolecular organization and function; they have been classified into several subfamilies in association with other ECM components.[8]

1. Fibrillar collagens (Collagens I, II, III, V, and XI)
2. Fibril-associated collagen with triple helices that are interrupted (Collagens IX, XII, XIV, XVI, XIX, XX, XXI and XXII.)
3. Beaded filaments of collagen (Collagen VI and XXVIII)
4. Collagen forming anchoring fibrils (Collagen VII))
5. Membrane-associated collagens(Collagens XIII, XVII, XXIII, and XXV)
6. Network-forming collagens (Collagens IV, VIII, and X)
7. Multiplexins (Collagens XV and XVIII.)

2.2. Proteoglycans

Proteoglycans are key organizing and functioning bio macromolecules found in tissues,made up of a protein core (biglycan, decorin, aggrecan, versican and prelecan) with negatively charged GAGs side chains that includehyaluronan (HA), heparan sulfate (HS), heparan (Hep), chondroitin sulfate (CS), keratin sulfate (KS), and dermatan sulfate (DS) (Figure 4). Most proteoglycans contain smaller oligosaccharides in addition to glycosaminoglycan chains and core proteins. These components may be linked to the proteoglycan core protein via O-glycosidic or N glycosidic linkages. The O-linked oligosaccharides are mostly found in chondroitin/dermatan sulfate-rich portion of proteoglycans, whereas the N-linked types are usually found in the portion of those core proteins that can bind to hyaluronan.[9]

PGs play both structural and biological roles in that they are responsible for the mechanical resistance to compression and hydration of the tissues, serve to trap growth factors (GFs) in the ECM, interact with other ECM molecules and cells, contributing to the formation of the ECM scaffold, and act as integrators of major signalling cascades governing cell behaviour.[6]

2.2.1. Biglycan

Biglycan is an interstitial proteoglycans that share homologous leucine rich core protein and has relatively wide distributions throughout most tissues and consists of two sites where glycosaminoglycan chain may attach. Biglycan is generally found in developing bone and cartilage, as well as in close association with cells such as keratinocytes and fibroblasts but lacks the ability to bind to collagens. Growth factors such as TGF-1 and growth hormone can influence biglycan expression. It exhibits significantly high expression levels in cancer tissues as compared with normal tissues thus can be indicated as a promising prognostic biomarker and therapeutic target agent.[10]

2.2.2. Decorin

Decorin has a similar size and structure to biglycan, except that it has only one site that can be substituted with a glycosaminoglycan chain.Decorin has a strong relationship with collagen type Ithat is mediated through proteincore rather than the glycosaminoglycan side chain. Decorin interacts with molecules in the matrix such as fibronectin and thrombospondin. It influences a wide range of biological processes, like cell growth, differentiation, proliferation, adhesion, migration, inflammation, fibrillogenesis, as well as cellular structure maintenance and signal transduction pathway regulation, culminating in anti-tumorigenic effects.[11]

2.2.3. Glycosaminoglycan

Glycosaminoglycans are unbranched, negatively charged, linear hetero-polysaccharides (polysaccharide consisting of more than one type of monosaccharide) containing a hexuronic acid or galactose repeating disaccharide structure in the case of keratin sulphate (KS). There are six types of glycosaminoglycans: the hyaluronic acid (HA), chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), heparan (Hep) and keratan sulfate (KS).[8]

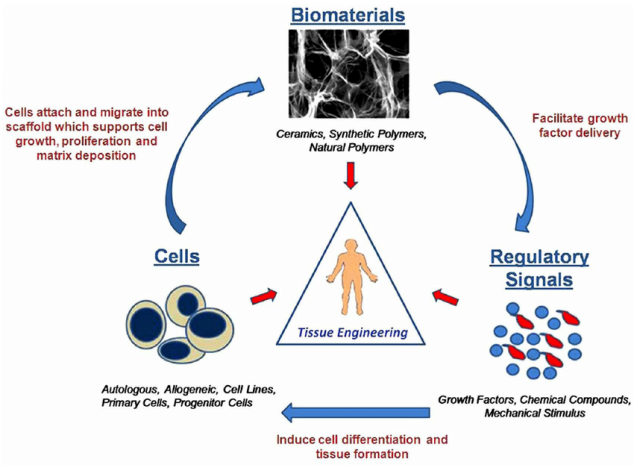


Fig. 1: Tissue engineering triad

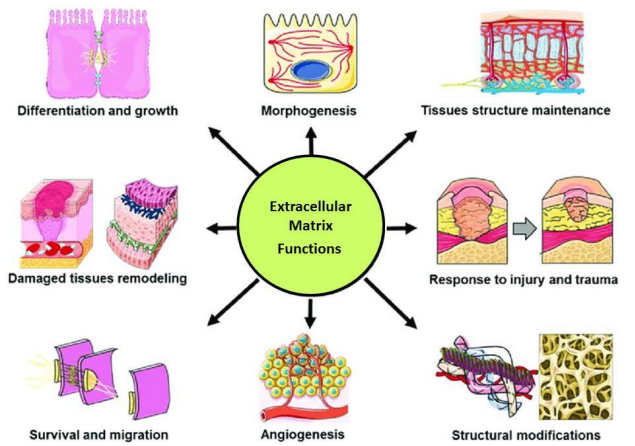


Fig. 2: Functions of extracellular matrix

2.2.3.1. Hyaluronic acid. Carl Meyer first described hyaluronic acid in 1934. HA is an unbranched GAG with a large molecular weight that is located intracellularly on the cell surface but mostly in the ECM. The simple structure and large molecular size of HA distinguish it from other GAGsdue to the fact that each HA disaccharide unit interacts with 25 water molecules; it has superior hydrophilic properties, which determine majority of its

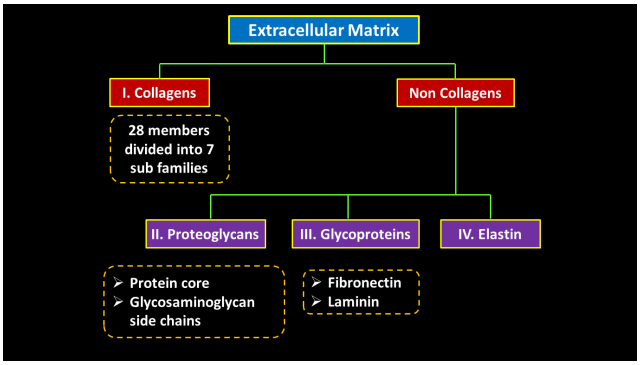


Fig. 3: Components of extracellular matrix

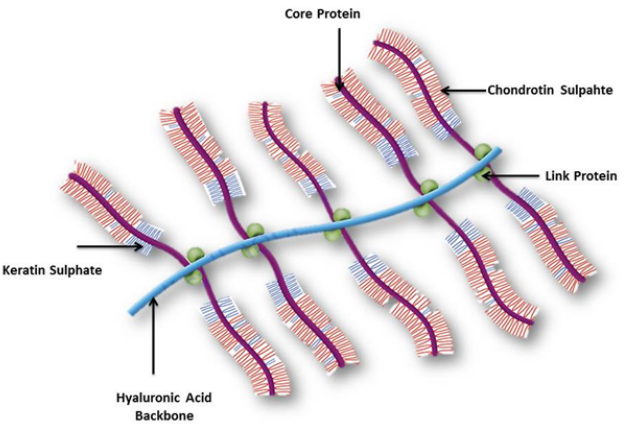


Fig. 4: Structure of proteoglycan

biomechanical properties. As a result, HA has evolved as one of the body's most physiologically active and relevant molecules. Due to its hygroscopic and viscoelastic properties, HA is an ideal component of vitreous fluid and joint fluid.[12]

In acute wounds, small HA fragments get accumulated at the site of injury activating the immune system to manage rupture in tissue integrity. In its native form HA also displays anti-inflammatory and immunosuppressive properties. Recently, the antioxidant properties of HA have been considered in a variety of pathologies, including osteoarthritis. Numerous studies have shown that HA signalling is important in the regulation of angiogenesis, primarily by influencing endothelial cell behaviour.[13]

2.2.3.2. Heparan and heparan sulfate. Heparan and heparansulphate are the most severe forms of a class of compounds known as heparan-like polysaccharides. The heparan molecule is strongly acidic and highly charged; its most significant biologic property is the ability to react electrostatically with proteins. The ability of heparan to bind various growth factors to ECM has given it a primary role in tissue and cellular function control such as growth, development, and repair.[8]

2.2.3.3. Keratin sulfate. Keratin sulphate differs from other glycosaminoglycans in that it lacks uronic acid. KS is found in cartilage, as well as other epithelial and neural tissues, where it contributes in wound healing, embryogenesis, collagen fiber construction, and corneal structure. KS is also identified in neurosecretory vesicles, showing that it is involved in vesicle production as well as neuronal activity[14]

2.3. Glycoproteins

Glycoproteins are proteins with oligosaccharide chains (glycans) covalently bonded to amino acid side chains.They are an essential integral membrane protein that participate in cell-cell interactions, act as lubricant and protective agents, and provides structural stability, in transport of molecules, hemostasis and immunity. Fibronectins and laminins are two groups of glycoproteins that significantly contribute in ECM formation and function.[8]

2.3.1. Fibronectin

Fibronectin is a glycoprotein that is synthesised by local cells and can operate as biological glue, allowing it to connect with other ECM components.[15] There are two types of fibronectin: a soluble dimeric form found in plasma and a multimeric cross linked form found in the ECM of most tissues as fibrils. It has glycosaminoglycan, integrin, collagen, and other ECM protein binding sites, as well as self-association sites.[16]

2.3.2. Laminin

Laminin is a highly interacting molecule that, through interactions with type IV collagen, contributes to the network structure of the basement membrane; they also interact with other ECM components like HS. Laminins act as important regulatory molecules for epithelial cells, endothelial cells and neuritesattachment, proliferation and differentiation. They play an important role in the creation and maintenance of vascular systems, making them ideal as tissue engineering scaffolds.[17]

Aside from these macromolecules that make up the majority of ECM, another protein that is present in modest amounts but plays a crucial function in ECM composition and tissue integrity is elastin.

In contrast to collagen, elastin provides elasticity to tissues, allowing them to stretch and then return to their former state. They are necessary for the normal functioning of many tissues that undergo reversible and recurring deformation, such as the arteries, skin, tendons, and lungs. Elastic fibers are composed of two separate morphological elements: a mantle of longitudinal arranged fibrillin-based microfibers plus a dense interior of cross-linked elastin, accounting for more than 90% of the fiber composition.[18] Elastic capabilities of the network are due to the hydrophobic domains of elastin.

ECM remodeling is an important method for directing cell differentiation, which includes stem cell niche generation and maintenance, radiating morphogenesis, angiogenesis, bone remodeling, and wound reconstruction. The removal of one or more of the ECM's components is an effective technique for remodeling it. Matrix Metalloproteases (MMPs) are the most important enzymes in ECM remodeling.[19]

3. Applications of ECM

The good effects and potential of ECM have been recognised over the years, and these are currently actively used in many therapeutic contexts, either as distinct entities or in conjunction with other materials. In Periodontology promising results have been obtained in all three types of perio-surgeries i.e. Regenerative Therapy, Periodontal Plastic Surgery and Implants. They have also found their way in facial rejuvenation procedure.

3.1. Regenerative therapy

Evidence has shown that ECM based materials when use in conjugation with regenerative modalities like bone grafts and GTR membranes promote cell growth and differentiation accelerates healing during initial phase of regeneration.

Over a 24-month period, Brigulioet al[20] investigated the efficacy of hyaluronic acid in the therapy of intrabony periodontal abnormalities. When compared to open flap debridement (OFD), intrabony defect locations treated with hyaluronic acid provided extra benefits in terms of clinical attachment level gain, pocket depth reduction, and predictability.

Deshpande et al[21] investigated the effects of incorporating organic collagen into a nanocrystaline hydroxyapatite (nHA) bone substitute for the repair of intrabony defects. Forty patients with chronic periodontitis who had at least one intrabony defect were treated surgically with OFD followed by grafting (Group A: 20 sites treated with nHA with organic collagen, Group B: 20 sites treated with nHA). The authors found that the presence of ECM - collagen in bone graft matrix explains the efficiency of nHA composite during the early healing phase.

3.2. Periodontal plastic surgery

Use of ECM in speeding wound healing and recession coverage techniques has gained traction. It has been demonstrated that they produce good clinical outcomes, enhance angiogenesis, and eliminate the requirement for an additional operative site, minimizing patient morbidity during such procedures.[22]

Harris[23] compared the efficiency of acellular dermal matrix (ADM) to CTG for root coverage. They concluded that there was no statistically significant difference in mean

root coverage between the two groups, and that the results of both treatments were aesthetically pleasing to the patients.

Nevins et al[24] compared the effectiveness and practicality of an ECM membrane (Dyna Matrix) to that of autogenous gingival graft to improve the dimension of keratinized tissue and concluded that DynaMatrix membrane may be used as a substitute for autogenous gingival graft in enhancing the dimensions of keratinized attached gingiva. The use of ECM membrane also provides an infinite reservoir of donor tissue, lowering patient morbidity.

3.3. Implants

Under the constant evolving field of dental implantology where focus has always been on ways to improve osseointegration, reconstructive implant surgery and promoting peri implant tissue health, regenerative properties of ECM can utilized to play a vital role in this process.[25]

Cryopreserved amniotic membrane was found to be helpful in increasing cicatrization, wound healing, and lowering discomfort in patients undergoing implant implantation in a randomized controlled research. ECM membranes are also being used as alternatives to soft tissue grafts for treatment of peri-implantitis and in soft tissue augmentation around implants.[22]

According to the findings of a systematic review and meta-analysis on whether the introduction of collagen-CS matrix in implant surfaces influences osseointegration, the integration of collagen-CS matrix in implant surfaces appears to promote osseointegration, and animal model results support phase I studies in healthy humans.[26]

3.4. Facial rejuvenation

Challenge of meeting the criteria for an ideal filler has led researchers down a number of development paths, one of which was the introduction of collagen and HA as filler materials. To reshape or enlarge the lips, HA fillers can be used in the body of the lips. Collagen fillers are only used in the vermillion border. Fillers containing HA are thought to last twice as long as those containing collagen.[27]

4. Conclusion

Extracellular matrix (ECM) is a highly dynamic 3D macromolecular framework that triggers critical biochmical and biomechanical stimuli essential for tissue remodeling.

Currently many ECM derived biopolymers are being used that are quick to react with host tissues, induce cell deposition and promote rapid angiogenesis and function essential for regeneration of lost tissues. Various authors have suggested that the use of these grafts poses challenges with respect to their stabilization and suturing on the recipient bed or insertion into a tunnel flap.

Future studies are being carried to develop a 3D ECM based synthetic model that may incorporate the features of nano self-assembly to create an ideal bio-ink that can serve as the mainstay scaffold material to be employed in the process of tissue engineering and thus achieve true periodontal regeneration.

5. Conflict of Interest

None.

6. Source of Funding

None.

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