The Collagen Family: Biosynthesis and Degradation - Oral Pathologies Induced by Genes Mutations

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Abstract: Mutations, deletion, insertions, and DNA splicing are involved in many pathologies of the oral sphere. Type I collagen is the major structural protein of bone and dentin. The genetic disease affects more than 1 in 10,000 individuals, and is characterized by fragile bones, skeletal deformities, frequent bone fractures, or even prenatal death. In addition to osteogenesis imperfecta (OI) and dentinogenesis imperfecta (DI), collagen mutations produce Ehlers-Danlos syndrome (EDS), and Alport, Marfan, and Good pasture syndromes. The different forms of the collagen super family include the fibril-forming collagens, collagen forming a network (basement membrane), membrane collagen, and anchoring fibrils. This family of molecules comprises 28 members. For type I collagen collagen is formed by α–chains, cross banded at regular intervals of 67nm. Synthetized as procollagen (with a N- and C-propeptide), the terminal extensions are cleaved by zinc-dependent endopeptidases. Hydroxyproline, hydroxylysine and glycine, are present at every third position. Epidermolysis bullosa are due to collagen gene mutations, or either to the gene coding for cellular cytokeratins (type K5 and/or K14). Mutations are reaching the extra cellular anchoring filaments of the basement membrane (involved in junctional EB),or mutations of the collagen located in the papillary and reticular layers (dystrophic EB - DEB). Osteogenesis imperfecta and some other bone pathologies are detectable in the oral cavity. Mutations od collagens, such as oral submucous fibrosis, diabetes mellitus, kidney and squamous cell carcinoma, are the consequences of genetic diseases involved directly in several areas of the body, or interfering indirectly with the tissues if the oral cavity. Some drugs improve the symptoms of the diseases.

Keywords: Mutations of collagen-coding genes, Fibrillogenesis, Extracellular assembly, Ehlers-Danlos syndrome, Osteogenesis imperfecta, Alport, Marfan, Goodpasture syndromes.

1. INTRODUCTION

The collagen super family comprises 28 members. Each molecule consists of three polypeptide chains, called α chains [1, 2].

This family includes specifically:

- Fibril-forming collagens (Type I, II, III, V, XI),
- Non-fibrillar collagens, comprising
  - Fibril-associated collagens with interrupted triple helix (Type IX, XII, XIV, XIX, XXI)(FACIT),
  - Network-forming collagens (Collagens IV, VI, VII, XXVI, and XXVIII),
  - Membrane associated collagens (MACIT).
  - Multiplexins (Type collagen XV and XVIII).

Collagens can be subdivided into subfamilies based on their supramolecular assemblies: fibrils, beaded filaments, anchoring fibrils and networks.

Proline hydroxylation is of crucial importance and induce the triple helical structure. The common characteristic of the collagen family is the presence of hydroxyproline and hydroxylysine and glycine, present at every third position. Glycosylation of hydroxylysine residues (glucose and galactose, established links to hydroxylisine). The repeating triplet Gly-X-Y is required for the formation of the triple helix. Aminoacid triplet constitute the collagen primary structure. In the absence of hydroxylation, the secretion of collagen is inhibited. It is assumed that glycine, because of its small size, allows the close association of the three α-chains. The three α-chains are held together by hydrogen bonds of hydroxyproline where as hydroxylysine enables the formation of fibrils by binding the tropocollagen molecules to each other (secondary structure) and contributes to collagen molecules triple helix formation (tertiary structure) and finally fibrils formation (quaternary structure) [3], with sites of attachment for short carbohydrate chains that are made up of glucose and galactose [4].

Intracellular Steps

Extracellular steps: NH2-terminal and COOH-terminal extensions called N- and C-propeptides are cleaved by procollagen peptidases. The proteolytic cleavage of the propeptide controls the process of fibril formation.

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The synthesis of a pro-α-chain requires two steps: firstly, a cellular and secondly an extracellular matrix stage:

inside the cell: It need 8 minutes to synthezise the preprocollagen. These steps implicate the intracellular assembly of pro-α chains in the cisternae of the RER, posttranslational hydroxylations and glycosylations , association and disulfide-bonding of C-propeptides. It was suggested that procollagen leave the endoplasmic reticulum and migrate to the Golgi region, where they are merging with secretory vacuoles.

outside the cells: The time needed for secretion is about 20minutes for type I procollagen and 60minutes for type IV. Exocytosis occurs by fusion of the vesicles with the plasma membrane. Procollagen peptidases cleave the amino terminal at the moment where the procollagen is leaving the cells, and convert in the outside extracellular marix the procollagen into native collagen after the cleavage of the C-terminal. Proteolytic processing of procollagen to collagen, self-assembly of fibrils by nucleated growth, and covalent cross-linking of the fibrils are occurring then.The fibres display cross banding at regular intervals of 67nm, and many micrometers in length [5, 6]. The molecules are staggered by ~ 67nm intervals [type I, II, III, V & XI].

The genetic mutations involved in Ehlers-Danlos disorders, display defects in type IV collagen leading to alterations of the kidney. In humans, the oral cavity shows dislocations of the temporo-mandibular joint, abnormal pulp shape, pulp calcification, and mucosal fragility [7]. The mutant mice displays some forms of dentinogenesis imperfecta, which has for consequences a reduction in incisor pulp chamber areas, and a reduced number of dentinal with irregularity of spacing [8].

Collagen Biosynthesis and Degradation

Collagen biosynthesis: The fibrils are synthetized as pro-α chains of collagen molecules. From part and other, the fibrils present the N- and C-:non-helical extensions.The pro-α-chains consist of a central collagenous region, (Gly-X-Y), and two amino N- and carboxy C- terminal noncollagenous propeptide regions. Non-helical N-telopeptide Secreted as Protein Acidic and Rich in Cysteine (SPARC). Is the intermediary form.The N-terminal is about # 20,000 and the C-terminal about #34,000 MW [9]. The N-propeptide is cleaved by a procollagen N-proteinases belonging to the Disintegrin and Metalloproteinase Family, with thrombspondin motifs (the ADAMTS family).

The pro-collagen C-proteinase (also termed Bone Morphogenetic Protein-1(BMP-1) is also implicated in the maturation of procollagen [2]. The amino-propeptide is released in the extracellular compartment. When the extensions are cleaved, the collagen molecule underwent its terminal fibrillation.

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases implicated in N- and C-terminal cleavage of the pro-collagen extensions.

The collagen molecule is a structural protein of the extracellular matrix (ECM) that contains one or more domains having the conformation of a collagen triple helix. It can be:

- Associated with type I collagen (skin, bone, dentin).
- Associated with type II: hyaline cartilage, vitrous body,
- Also present as fibril-associated collagens with interrupted triple helices (FACITs): collagen IX.
- Some collagens are forming sheets: Basement membrane type IV and VIII collagens (the skin basement membrane, Descemet's membrane of the corneal epithelium formed by type VIII collagen, and type X collagen).
- All of them may be involved in pathologic fibrillation.
- Mutations of Type VII collagen, forming anchoring fibrils leads to the separation between epidermis and dermis and to blister formation.

Matrix metalloproteinases (MMP) is a large family of proteolytic enzymes that includes:

collagenases (MMP-1, 8, 13), gelatinases (MMP-2, 9), metalloelastases (MMP-12), stromelysins (MMP-3, 10, 11),matrilysin (MMP-7),all of them being involved in the degradation of collagens. Collagenase 1, 2 and 3 degrades type I, II, III, V collagens. Collagenase 3 can deteriorate type I, II, III, IV, IX, X,XI collagens, fibronectin and other extracellular matrix component. Stromelysins (MMP-3, MMP-10, and MMP-11 are degrading proteoglycans, basement membranes, laminin and fibronectine.

Mutations in collagen genes are the causes of rare and some common diseases in humans-

implicating genetic and acquired diseases of collagens [1, 10]:

Mutations of collagen genes include deletion, insertions, DNA splicing mutations. The synthesis of structurally defective pro-α chains interfere with the zipper like folding of the collagen triple helix and the self-assembly of collagen fibrils.

Two other types of fibrils have been identified. Anchoring fibrils are located in dermo-epidermic junctions and transmembrane collagen (BP180kDa protein) They play also role in the fibrillation process, and their mutations implicate a series of pathologic diseases.

2. ORAL PATHOLOGIES DUES TO MUTATIONS OF THE COLLAGEN GENES: CLINICAL FEATURES

Osteogenesis imperfecta (fragility of bone) [4]. The clinical features commonly observed in patients with osteogenesisimperfecta include abnormal bone formation, growth deficiency, bone fragility, blue sclerae, hearing loss, skin thinness, joint laxity and hypermobility and dentino genesis imperfecta. There are 19 recognized forms of osteogenesis imperfecta. In

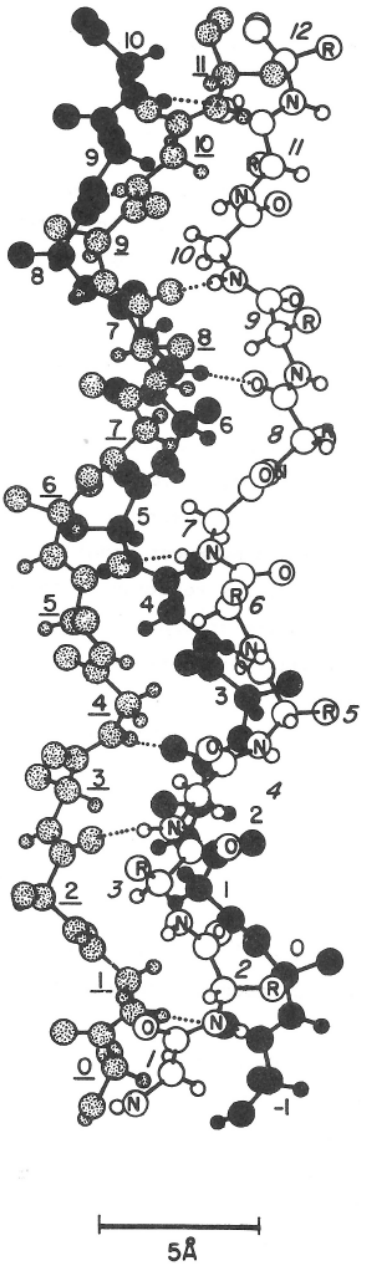

Figure 1: Triple helix conformation of collagen [11].

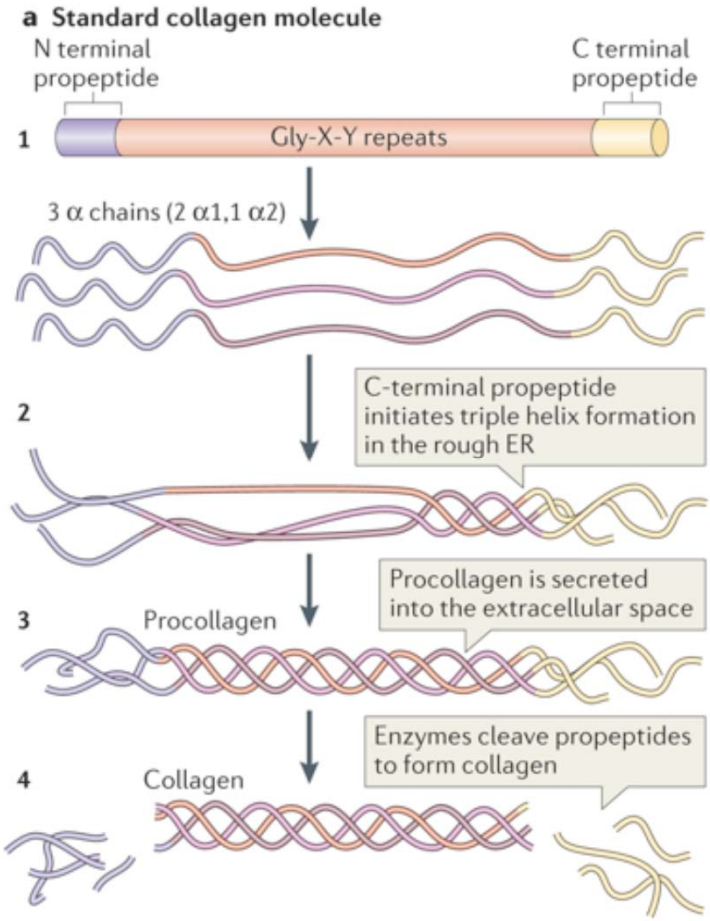

Figure 2: Collagen fibrils molecule: from the pro-collagen (with N-terminal and C-terminal) to collagen [1, 2, 12].

Figure 3: Collagen fibers located in intertubular dentin; TEM. Ultrathin section stained by uranyl acetate and lead citrate.

addition, some defects have been identified: short stature, curvature of the spine, and disorders of tooth development (dentinogenesis imperfecta).

Also named glass bone disease (1-5/10 000) OI is due to mutations in the COL1A1 and COL1A2 genes encoding the alpha1 and alpha 2 chains of type I collagen.The genes are located on chromosome 17 and 7.

Ehlers-Danlos syndrome is a clinically and genetically heterogeneous connective tissue disorder characterized by skin hyper extensibility, hypermobility of joints and tissue fragility. At early onset, generalized periodontitis is one of the most noteworthy oral manifestations of the syndrome resulting in the premature loss of deciduous and permanent teeth. Hypoplasia of the enamel is commonly seen. Premolar and molar teeth may present deep fissures and long cusps. The teeth seem to be fragile and with some times microdontia [13].

Tenascin mutations: The tenascins are a family of large matricellular proteins of unknown function. The three family members described in mammals are tenascin-C (TNC, formerly cytotactin, or tenascin), tenascin-R (TNR, restrictin) and tenascin-X (TNX). All family members share a modular structure consisting of an NH_2-terminal sequence responsible for oligomerization of TNC, TNR, and possibly TNX; a variable number of cysteine-rich EGF-like repeats; the repeats being similar to the type III repeats of fibronectin and a COOH-terminal fibrinogen-like domain. Gene knockouts of three small leucine-rich proteoglycans (SLRPs), decorin, fibromodulin, and lumican are also implicated in this pathology. The phenotypes of all three knockouts include derangements in collagen fibril morphology. Curiously, the fibril abnormalities are quite different in the three animal models. Fibromodulin-null fibrils are smaller than wild-type fibrils and lumican-null fibrils are somewhat larger than normal, while decorin-null fibrils are of similar size but have greater size variation than normal fibrils. In the case of decorin and lumican, the defect in fibrillogenesis is accompanied by clinically apparent skin hyper extensibility and a striking reduction in skin tensile strength. Further support for these genes as candidates for EDS comes from the observation that all of these proteins are fibril-associated and the observation that SLRPs at the surface of the fibril appear to limit fibril growth and lateral fusion of fibrils. Clearly, testing of patients for mutations of these genes is warranted. Radiographic examination often divulges pulp stones and roots that are short and deformed [7, 14].

In man, dominant Ehlers-Danlos syndrome form VIII induces severe generalized periodontitis, alveolar bone lysis, premature loss of teeth. Autosomal recessive E-D syndrome don't seems to have an impact on the tissues of the oral cavity [9].

The following four syndromes have indirect consequences on oral tissues. They include:

- **Alport syndrome** Alport syndrome is a generalized inherited disorder of basement membranes, particularly those of glomeruli that involve type IV collagen. The mutations occur in the gene located on the X chromosome. Inherited defect of the classical X-linked Alport syndrome affects the α-5 chain of collagen type IV collagen gene (COL4A5) while the α-3 and α-4 chains of collagen type IV collagen genes (COL4A3 and COL4A4) are responsible for less frequent recessive forms of Alport syndrome. Itis characterized by renal impairment, loss of hearing and lens abnormalities, hypertension, hematuria and proteinuria.

- **Marfan syndrome**. Its incidence is 1-5/10 000 individuals. It is caused by an autosomal dominant mutation of the gene encoding fibrilline-1. Patients are tall and thin, with retinal detachment and lens displacement. Ocular complications can lead to blindness.

- **Goodpasture syndrome** Goodpasture syndrome is a rare but serious autoimmune disease that attacks the lungs and kidneys. The disease occurs when the body's immune system mistakenly produce santibodies against collagen in the lungs and kidneys. The first signs of Good pasture syndrome may include, fatigue, nausea and vomiting, difficulty breathing and pale skin.

- **Stickler syndrome** displays premature osteoarthritis, retinal degeneration, hearing loss and orofacial abnormalities. This is caused by mutations in the COL2A1, COL1A1, and COL11A2 procollagen fenes of type 2 and 11 collagen [4].

Pathology interferIng with the oral cavity: These alterations include defects in dentin (type I collagen), pulp (types I and III collagens), cementum (Types V, VI, and XIV collagens) periodontal ligament (type I, III and XIII collagens), basement membrane (type IV in the lamina densa, and type VII for anchoring fibrils).

Epidermolysis bullosa results from mutation specific of K5 or K14 genes and genes coding for

laminin. Prevalence: 1-9/100 000. Anatomo-pathology: Intraepidermal blisters are formed.

When the gene coding for type VII collagen is abnormal or missing, the formation of anchoring fibrils is impaired. A shortage of these fibrils disrupts the connection of the epidermis to the dermis, and friction or other minor trauma may cause the two skin layers to separate [15]. Four major forms have been identified: epidermolysis bullosa dystrophica (COL7A1)(DEB), junctional (JEB), simplex (EBS), and aquisita, involving different genes.

A number of factors modulating collagen synthesis are shown in Figure **3** [15].

Drug Therapy

Calcitonin

A single injection results in an immediate decrease in urinary hydroxyproline reflecting an acute inhibition of bone resorption. Chronic treatment osteolytic lesions are reversed. Bone biopsies exhibit a reduced number of bone cells, a decrease in marrow fibrosis, and a reduction of woven bone volume.

Bisphosphonates

The primary effect of bisphosphonates is to inhibit osteoclastic bone resorption, which *in vivo* is followed by a secondary decrease in bone formation. The earliest bisphosphonates which were developed,

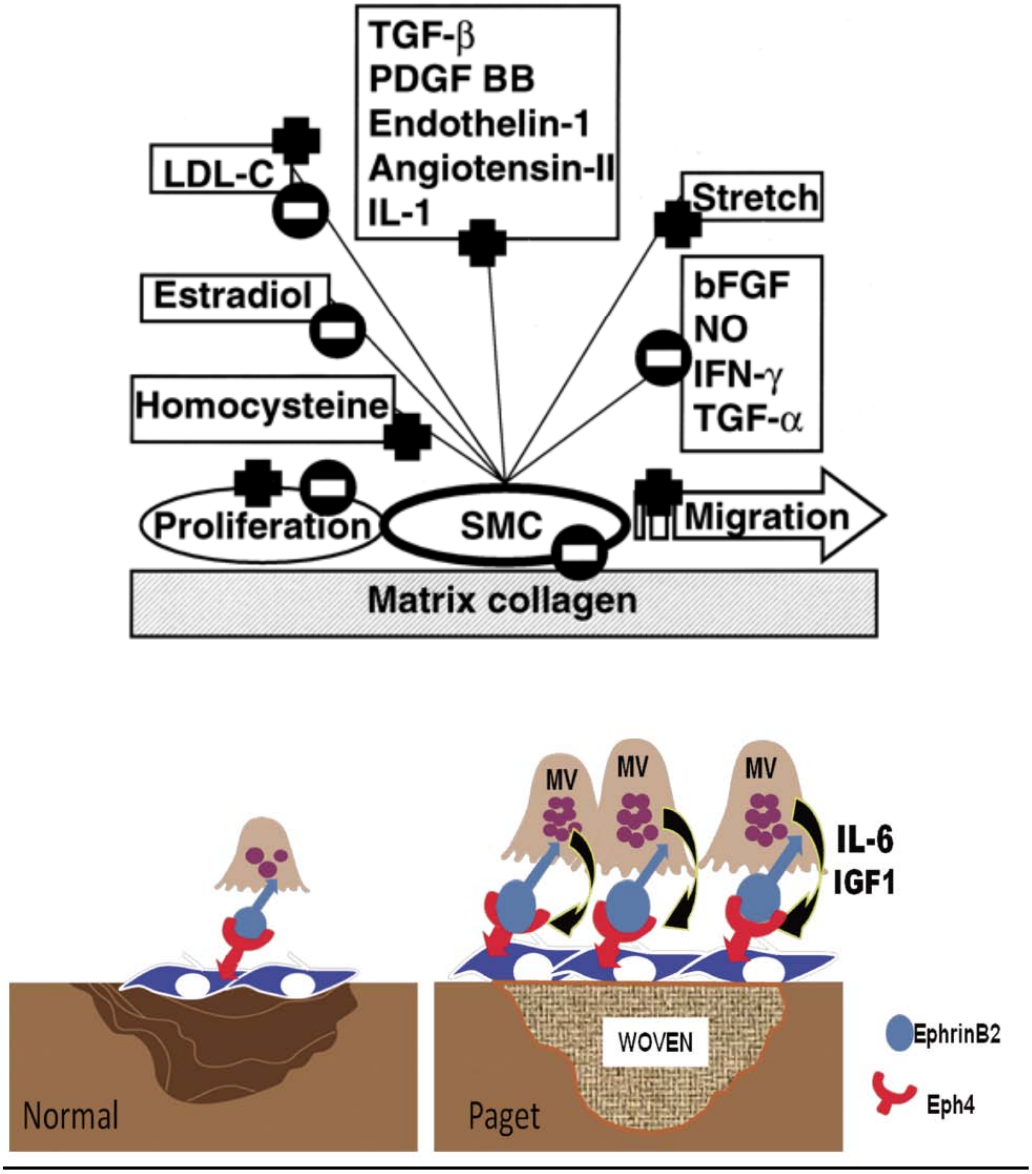

Figure 4: [16].

etidronate and clodronate, appear to achieve their effects by generating non-hydrolyzable analogues of adenosine triphosphate, while the later generation of more potent amino bisphosphonates, such as pamidronate and risedronate, inhibit protein prenylation through inhibition of farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway [17].

CONCLUSIONS

Mutations, deletion, insertions, DNA splicing mutations of the collagen genes cause alterations of collagen fibrillation and subsequently induce pathologies of the connective tissue [18]. Some well-identified syndromes are summarized in this review, including osteogenesis imperfecta, and collagen-forming sheaths. Ehlers-Danlos syndrome, Alport, Marfan and Goodpasture syndromes, are also implicated in diseases related to the oral cavity, but to a lesser extend. Epidermolysis bullosa constitute another series of pathologies due to collagen gene mutations [2, 19]. Intracellular synthesis, anchoring fibrils, and basement membrane, are subjected to genetic mutations. Drugs therapy, are efficient such treatment aiming to improve the incidence of these pathology on the pain, health and tolerability of the diseases for patients [19]. Some drugs may also correct pain and adverse effects, but not cure the disease resulting from genes mutations.

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