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Dentin biomodification: strategies, renewable resources and clinical applications

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ABSTRACT

Objectives. The biomodification of dentin is a biomimetic approach, mediated by bioactive agents, to enhance and reinforce the dentin by locally altering the biochemistry and biomechanical properties. This review provides an overview of key dentin matrix components, targeting effects of biomodification strategies, the chemistry of renewable natural sources, and current research on their potential clinical applications.

Methods. The PubMed database and collected literature were used as a resource for peer-reviewed articles to highlight the topics of dentin hierarchical structure, biomodification agents, and laboratorial investigations of their clinical applications. In addition, new data is presented on laboratorial methods for the standardization of proanthocyanidin-rich preparations as a renewable source of plant-derived biomodification agents.

Results. Biomodification agents can be categorized as physical methods and chemical agents. Synthetic and naturally occurring chemical strategies present distinctive mechanism of interaction with the tissue. Initially thought to be driven only by inter- or intra-molecular collagen induced non-enzymatic cross-linking, multiple interactions with other dentin components are fundamental for the long-term biomechanics and biostability of the tissue. Oligomeric proanthocyanidins show promising bioactivity, and their chemical complexity requires systematic evaluation of the active compounds to produce a fully standardized intervention material from renewable resource, prior to their detailed clinical evaluation.

Significance. Understanding the hierarchical structure of dentin and the targeting effect of the bioactive compounds will establish their use in both dentin-biomaterials interface and caries management.

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1. Overview

Dentin is a complex mineralized tissue arranged in an elaborate 3-dimensional framework composed of tubules extending from the pulp to the dentin–enamel junction, intra-tubular, and peri-tubular dentin. The mineral portion is composed of carbonate apatites. Fibrillar type I collagen accounts for 90% of the organic matrix, while the remaining 10% consists of non-collagenous proteins, such as phosphoproteins and proteoglycans (Fig. 1). The peri-tubular dentin, i.e., dentin surrounding the tubules, is highly mineralized (95 vol% of mineral), while most organic content is localized at the inter-tubular dentin (30 vol% of mineral) [1]. Dentin undergoes modifications by physiological aging and disease processes to produce different forms of dentin [2]. This process affects the biomechanics and biochemistry of the tissue.

Although similar in composition to bone, dentin does not share the same ability to remodel. This limits site regenerative therapies. An advantage of dentin over enamel is the presence of a collagen based scaffold that provides an appropriate cell-free backbone for tissue repair and regeneration. The presence of such a scaffold is a key to advance new concepts in tissue engineering approaches to the treatment of missing hard tissue. Recently, biomodification of dentin has been investigated as a biomimetic strategy therapy to mechanically strengthen the existing collagen network and also control biodegradation rates of extracellular matrix (ECM) components. This review provides an overview of important extracellular matrix components of dentin, as well as mechanisms and application of dentin biomodification, and specifically addresses the broad application of naturally occurring biomodification agents.

2. Extracellular matrix components relevant to dentin biomodification

2.1. *Type I collagen*

Fibrillar collagen is a strong and elastic biomaterial arranged into highly organized hierarchical structures [3,4]. Type I collagen is the most abundant of all collagen types and is defined as a coiled-coil trimer molecule, each of which is composed of the repeated sequence of amino acids Gly-X-Y, where X and Y are commonly found to be proline and hydroxyproline, respectively. Type I collagen molecules are biosynthesized from a larger precursor, procollagen, by cleavage at both its C- and N-terminal ends. The collagen fibrils are formed by spontaneous self-assembly of the molecules into a periodic structure with 67–69 nm repeat period overlap between neighboring molecules, which is crucial for the development of covalent inter-molecular cross-linking. The inter-molecular cross-linking, the final post-translational modification of collagen, is the basis for the stability, tensile strength and viscoelasticity of the collagen fibrils (Fig. 1). The slope of elastic stress-strain curve for collagen fibers increases with increased degree of cross-linking [5], and subtle perturbations to the cross-linking profile have been correlated with the strength of hard tissue [6]. In addition, the biodegradability and thermal stability of the tissue is also controlled by the amount and type of collagen cross-linking.

Endogenous collagen cross-linkings are mediated by enzymatic and non-enzymatic reactions. Enzymatic intra- and inter-molecular cross-links, formed between telopeptides and adjacent triple helical chains through lysine–lysine covalent bonding [6–8], are controlled by a number of factors, such as lysine hydroxylation, glycosylation, turnover rate, molecular packing, and external forces [9]. Non-enzymatic collagen cross-linkings are mediated by oxidation and glycation processes [10]. *Exogenous collagen cross-linking* can be induced by non-enzymatic reaction sources such as chemical agents and physical methods, both of which have distinct mechanisms of interaction with type I collagen (see Section 3.1).

2.2. *Proteoglycans*

Proteoglycans (PGs) are a major group of non-collagenous proteins identified in both pre-dentin and dentin. PGs play a crucial role in dentin mineralization [11,12] and the structural integrity of collagen fibrils [13]. They are classified into two distinct categories: the large aggregating chondroitin/keratan sulfate family, composed of molecules such as versican and aggregan, and the family of small leucine-rich proteoglycans (SLRPs) [14–16]. PGs found in dentin are mainly small leucine-rich collagen-binding carrying chondroitin-sulfate (CS, e.g. biglycan or decorin) with a limited distribution of keratan-sulfate (KS, e.g. fibromodulin, lumican) glycosaminoglycans chains (GAGs) [17]. Although there are similarities in the structure of decorin and biglycan, they differ in the pre-dentin/dentin distribution [18,19] and in related gene-expression during tooth mineralization [20]. In addition to their roles in mineralization, PGs control the tissue hydration and molecule diffusivity [21]. Hence, modified forms of the tissue, such as sclerotic dentin, can affect the distribution of PGs [22].

2.3. *Endogenous proteases*

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases; able to degrade different components of the ECM [23]. In the oral cavity, MMPs are linked to periodontal disease, caries progression, pulp inflammation and cancer [24–26]. In the dentin–pulp complex, several MMPs have been identified such as MMP-2, -3, -8 and -9 [27–29]. Another important family of proteases are the cysteine cathepsins [30,31]. Cathepsins belong to the papain family and were initially considered as lysosomal proteases, although they can act extracellularly [32]. They become active at acidic pH and most are endopeptidases, with some exceptions like cathepsin B that can also act as a carboxypeptidase [33]. Cathepsins participate in ECM degradation in physiological and pathological processes like bone remodeling, inflammation, rheumatoid arthritis, diabetes, multiple sclerosis and cancer [32,34]. In addition to their role in caries progression [30], cathepsins have also been associated with other oral diseases such as periodontitis, bone resorption and oral cancer [35–37]. Like

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