

Breakthroughs and Views

Collagen overglycosylation: A biochemical feature that may contribute to bone quality

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Abstract

Skeletal ability to resist mechanical stress is determined by bone amount and quality, which relies on macro- and micro-architecture, turnover, bone matrix, and mineralisation; the role of collagen has not been clearly elucidated. Numerous post-translational steps are involved in collagen type I biosynthesis, including residue hydroxylation and glycosylation catalysed by enzymes that work until the protein folds forming the triple helix; therefore, folding rate regulates these processes. Overglycosylated hydroxylysines are poor substrates for ϵ -amino group deamination which initiates cross-link formation. Three clinical conditions associated with fractures may relate collagen overglycosylation with bone quality: (i) *Osteogenesis Imperfecta*, in which genetic mutations distort triple helix conformation and slow folding rate favouring overglycosylation; (ii) diabetes mellitus, with collagen overglycosylation by AGE accumulation; and, (iii) menopause, according to experimental studies demonstrating ovariectomy-related trabecular bone collagen overglycosylation preventable by 17β -estradiol or tamoxifen. Specific actions on collagen of drugs used for bone protection should be explored in future studies.

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The function of the skeleton, as an antigravity scaffold capable of resisting mechanical stress, is determined by the amount of bone and by the type of tissue structure able to best exert bone resistance, generally defined as “bone quality.” Bone quality relies on different parameters, such as the macro-architecture, micro-architecture, turnover rate, bone matrix, and mineralisation [1]. While each of these is essential for a good quality of bone, the crucial role of collagen, the main component of the bone matrix upon which all of the above-mentioned parameters depend to some extent, has not been clearly elucidated.

Collagen biosynthesis and fibril formation

A large number of intracellular post-translational processing steps are involved in the biosynthesis of type I procollagen. They include hydroxylation of prolyl residues, hydroxylation of lysyl residues, and glycosylation of some hydroxylysine residues with galactose and glucosylgalactose [2]. All the reactions are catalysed by specific enzymes that work until the protein folds into the triple-helical conformation. As a consequence, the degree of modification of the protein is regulated by its rate of folding [3] (see Fig. 1).

Once the mature molecules are formed, they assemble into fibrils, the functional supramolecular structural framework. In fibrils, molecules of collagen are parallel to each other and the three strands forming the triple helix

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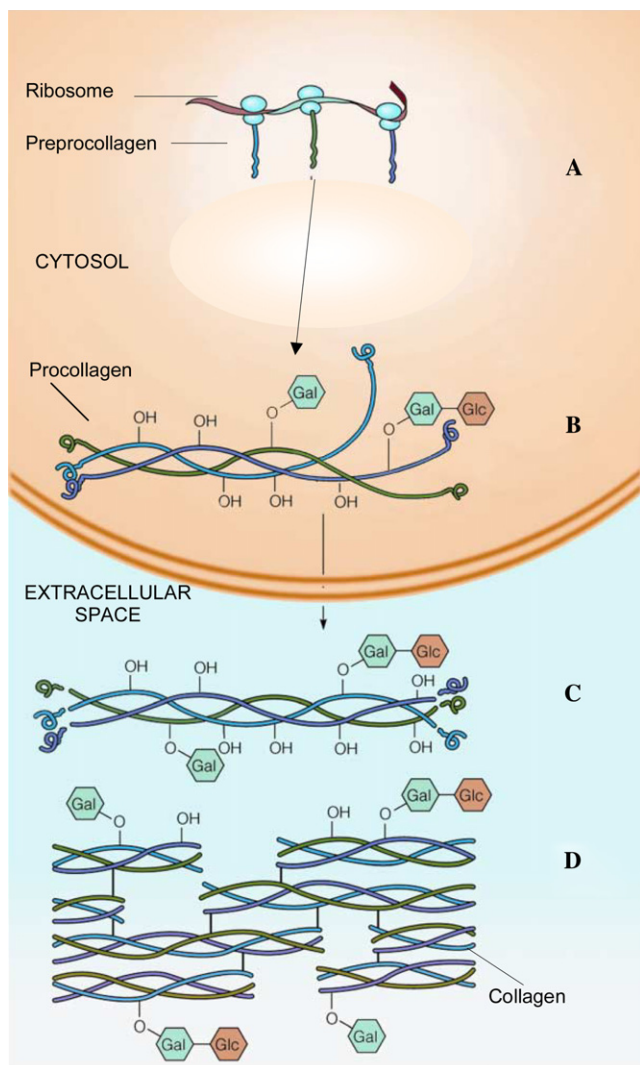


Fig. 1. Biosynthesis of collagen molecule. The process of collagen synthesis is schematically presented as a consecutive series of steps from (A) to (D). Steps (A) and (B) take place in the cytosol while steps (C) and (D) are extracellular processes. (A) Procollagen biosynthesis. (B) After the release of α -1 and α -2 chains from the ribosome, the formation of the triple helix occurs through a zipper-like mechanism initiating at the COOH-terminus of the protein and propagating to the NH_2 terminus. Hydroxylation of prolyl and lysyl residues, and glycosylation of hydroxylysine residues take place and its extent depends on the rate of folding. (C) Extracellular transport, and amino- and carboxy-terminal propeptide cleavage by specific proteases leaving the triple helical domain molecule which assembles into fibril. (D) Oxidative deamination of ϵ -amino groups of lysines and hydroxylysines, forming allolysines and hydroxyallolysines, catalysed by the ϵ -amino lysyl-hydroxylysyl deaminase for the subsequent and spontaneous formation of nonreducible pyridinoline and deoxypyridinoline cross-links.

overlap by multiples of 67 nm. Each strand is 300 nm long and there is a 40 nm gap between the end of one and the beginning of the successive one in the triple helix. In bone, the hydroxyapatite crystals lie in the 40 nm gaps between successive collagen molecules forming the fibril [2].

To detail the effects of the extent of lysine hydroxylation and hydroxylysine glycosylation on fibril formation, the group of Kivirikko studied in vitro the formation of fibrils of a recombinant human type II collagen produced in insect cells. The experimental model provided conclusive evidence in favour of the hypothesis that the degree of glycosylation determines fibril diameter, orientation, organisation, and resistance to mechanical stress [4].

In addition to the diameter as a determinant of the mechanical resistance and the tensile strength of the fibrils, another very important determinant is the type and the number of cross-links within and between the collagen molecules forming the fibril. The last post-translational modification of the collagen molecule, which occurs extracellularly, is the oxidative deamination of the ϵ -amino groups of lysines and hydroxylysines, forming allolysines and hydroxyallolysines, catalysed by the ϵ -amino lysyl-hydroxylysyl deaminase [5]. This is the only enzymatic step necessary for the formation of the nonreducible cross-links pyridinoline and deoxypyridinoline; the rest of the reactions of the pathway occur spontaneously until the pyridinium ring is formed. Interestingly, the hydroxylysines that are linked to a sugar are poor substrates for the deaminase. Therefore, the higher the glycosylation, the lower the pyridinium cross-links and in turn, the lower the tensile strength of the fibril. Hence, an overglycosylation of the collagen molecule results in a lower diameter and a lower cross-link number, with as a consequence a lower stabilisation of the fibril and an impaired resistance of the structural framework (see Fig. 1).

The *Osteogenesis Imperfecta* model: “the disease of brittle bone”

Osteogenesis Imperfecta is a genetic disease due to a mutation in the coding sequences of either pro- α 1 gene or pro- α 2 gene. Over 50 mutations that substitute amino acid residues with bulkier side chains for glycine residues have been defined in patients with various forms of *Osteogenesis Imperfecta* [6]. Replacement of a glycine residue (one Gly every third position makes the event very probable) with a bulkier amino acid distorts the conformation of the triple helix, because each of the glycine residues in the repetitive Gly-X-Y sequence of collagen is located in the sterically hindered position in the centre of the triple strand. The consequence of the mutation, in terms of the amount of post-translational modification, depends upon the position on the primary structure and upon the amino acid that substitutes the glycine. This can lead to three situations: (i) the structural abnormality can prevent the complete folding of the three chains in the triple helix, with the consequence that the chains will be degraded

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