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RESEARCH ARTICLE

BASICS OF COLLAGEN

Farhana Ashraf., Ajit V.Koshy., Vidya M., Prachi Baldwan and M. Abu Bakr

M.A Rangoonwala College of Dental Sciences & Research Centre, Pune

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ABSTRACT

Collagen is the main structural protein component of extracellular matrix of the connective tissue in humans, making upto 25% to 35% of the whole-body protein content. Collagen arranged in elongated fibrils is found in fibrous tissues like tendons, ligament, skin as well as in bones, cartilage, muscle and dental tissues. Depending upon the degree of mineralization, collagen tissues could be rigid (bone), compliant (tendon) or in between rigid to compliant (cartilage). The fibroblast is the most common cell that is responsible for the formation of collagen. The biosynthesis of collagens starting with gene transcription within the nucleus to the aggregation of collagen heterotrimers into large fibrils is a complex multistep process. Degradation of collagen takes placeintracellularly and extracellularly. Microscopically, collagen is demonstrated by various histochemical stains. It has a triple helical structure, composed of three interwined polypeptide chains. It is important to health as it forms the major component of many vital tissues in body and is essential in maintenance of structure and function of body.

INTRODUCTION

Connective tissue comprises a diverse group of cells within a tissue-specific matrix. The extra cellular matrix (ECM) includes structural (fibers) and specialized proteins which constitute the ground substance. Connective tissue forms a vast and continuous compartment throughout the body, bounded by the basal laminae of the various epithelia and by the basal or external laminae of muscle cells and nerve-supporting cells. The functions of the various connective tissues are reflected in the types of cells and fibers present within the tissue and the composition of the ground substance in the ECM. The fibrous components of the extra cellular matrix are produced by fibroblasts and classically divided into collagen fibers, reticular fibers and elastic fibers[1].

Each type of fiber is composed of protein consisting of long peptide chains. The most abundant proteins in the extracellular matrix are members of the collagen family.[2] The term 'collagen' is in fact derived from the Greek word for glue and was initially used to describe that constituent of connective tissue which yields gelatin on boiling.[3] There is no agreed definition for a collagen; there are triple helical proteins that are called collagens and there are proteins that have triple helical domains that are not regarded as collagens. In general, collagens are regarded as triple helical proteins that have functions in tissue assembly or maintenance. Inevitably, the line between 'collagens' and 'collagen-like' proteins is blurred. Collagens are widespread throughout the body such as in tendon, cartilage, bone, skin and also in basement membranes. They are important for a broad range of functions, including tissue morphogenesis, tissue scaffolding, cell adhesion, cell migration, angiogenesis, tissue repair and even cancer.[4]

Types of Collagen

Fibroblasts

Fibroblasts are the predominant cells of connective tissue. They are responsible for the formation and maintenance of the fibrous components and the ground substance of connective tissue. Fibroblasts usually are recognized by their association with collagen fiber bundles. The resting fibroblast (fibrocyte) is an elongated cell with little cytoplasm and a dark-staining, flattened nucleus containing condensed chromatin. Active fibroblasts have an oval shaped, pale-staining nucleus and a greater amount of cytoplasm, the degree of synthetic and secretory capacity of fibroblasts is evidenced by the amount of rough endoplasmic reticulum, secretory granules, and mitochondria, and the extent of the Golgi complex in their cytoplasm. Fibroblasts exhibit motility and contractility, which are important during connective tissue formation and remodelling and during wound repair. Fibroblasts are separated from one another by the extracellular matrix components; therefore, intercellular junctions are not present. They form specialized focal contacts with components of the

extracellular matrix, called a fibronexus. Fibroblasts can replicate by mitosis when they are differentiated.[5]

Collagen type	Principle Tissue Distribution	Cells of Origin
I	Loose and dense ordinary connective tissue; collagen fibres	Fibroblasts and reticular cells; smooth muscle cells
	Bone	Osteoblasts
	Dentin	Odontoblasts
II	Hyaline and elastic cartilage	Chrondrocytes
	Viterous body of the eye	Retinal cells Fibroblasts and reticular cells
III	Loose connective tissue; reticular fibres	Fibroblasts and reticular cells
	Papillary layer of dermis	Fibroblasts
IV	Basement membranes	Epithelial and endothelial cells
	Lens capsule of the eye	Lens fibre
V	Fetal membranes; placenta	Fibroblasts
	Basement membranes	Epithelial cells
	Bone	Osteoblasts
	Smooth muscle	Smooth muscle cells
VI	Connective tissue	Fibroblasts
VII	Epithelial basement membranes; Anchoring fibrils	Fibroblasts and keratinocytes
VIII	Cornea	Corneal fibroblasts
IX	Cartilage	Chondrocytes
X	Hypertrophic zone of cartilage growth plate	Chondrocytes
XI	Cartilage	Chondrocytes
XII	Papillary dermis	Fibroblasts
XIII	Epidermis	Fibroblasts
XIV	Reticular dermis	Fibroblasts
XV	Epithelial and endothelial basement membranes	Epithelial cells

Collagen Biosynthesis

The biosynthesis of collagens starting with gene transcription within the nucleus to the aggregation of collagen heterotrimers into large fibrils is a complex multistep process.

- In the nucleus, genes for pro alpha chains are transcribed on mRNA.
- mRNA is translated into rough endoplasmic reticulum (RER) into pre-pro collagen.
- In RER, signal sequence is removed from N-terminal; pre-procollagen is now known as pro-peptide.
- Proline and lysine residues are hydroxylated via enzymes prolyl hydroxylase and lysyl hydroxlylase. This step requires vitamin C as co-factor.
- Glucose and galactose are added to hydroxyl group of lysine (but not onto proline). This process is called as glycosylation.
- Hydroxylated and glycosylated propeptides will twist around each other to form a triple helix known as procollagen. Twists are located at center of molecules and chains are loose at the end.
- Procollagen is packed in vesicles and transported to golgi body for further processing.
- Self-assembly of tropocollagen into fibrils with further crosslinking eventually forms the mature collagen molecule.

Mechanism Degradation of Collagen

Degradation of collagen is essential for certain aspects of normal embryonic development, tissue morphogenesis and remodeling and also occurs during wound repair, inflammatory diseases, and tumor growth and metastasis.[5]

Two mechanisms have been recognized for the degradation of collagen

1. Extracellular degradation*:* The collagen triple helix is highly resistant to proteolytic attack. The matrix metalloproteinase (MMP), a large family of proteolytic enzymes that includes collagenases, gelatinases, metalloelastase, stromelysins, and matrilysins, and in addition to these secreted enzymes, several membrane-type (MT) MMPs exist. MT-MMPs have transmembrane domains and extracellular active sites.

2. Intracellular degradation

- Binding of the collagen fibril to the Integrin receptor on the fibroblast.
- Partial digestion and fragmentation of the fibril by the action of Gelatinase A.
- Phagocytosis of the fragments and formation of a phagolysosome.
- Intracellular digestion of these fragments in the acidic environment of the phagolysosome by the action of lysosomal enzymes particularly Cathepsins.[5]

Structure of collagen

The characteristic structure of collagen molecules has been proposed over 50 years ago on the basis of X-ray diffraction[6]. Three polypeptide alpha (α) chains are closely packed into a right-handed twisted helix. The triple helix has two small non-helical domains (telopeptides) located at each end of the molecule. The close packing into a triple helix is mediated by the high content of glycine (Gly) residues[7]. Gly occupies every third position in the amino acid sequence of each α-chain and is always positioned in the core of the triple helix[8,9]. This results in the motif (Gly-X-Y), where X and Y are occupied by other amino acids[10]. Finally, stabilization of the triple helix into a collagen molecule is mediated by hydrogen bonds[11] as well as hydroxylation of the proline and lysine residues formed between the α-chains[12].

Staining of Collagen

Unstained collagen fibres of connective tissue are usually less than 10μm in diameter and are colorless. Collagen fibres appear as long, wavy, pink fibres bundles when stained with routine hematoxylin and eosin. Ultra-structural view of collagen fibres stained with heavy metals display cross banding at regular intervals of 67nm which is a characteristic property of these fibres.[13]

Various special stains have been used to demonstrate collagen fibres which include Van Gieson, Masson's trichrome, Weigert's Resorcin Fushin, modified Movat's stain, Goldner's trichrome method, Wilder modification of Bielschowsky's method etc.[14] Puchtler and colleagues found Sirius red F3BA (Color Index 35780) dissolved in a saturated picric acid solution consistently stained thin collagen fibers, did not fade, and was suitable for use with polarized light microscopy.[15]

CONCLUSION

Collagen being the single most abundant protein in the animal kingdom forms the major structural element of all connective tissues as well as in the interstitial tissue of virtually all parenchymal organs, where they contribute to the stability of tissues and organs and maintain their structural integrity. Research on the collagen structure, organization and remodeling, help us understand better the importance of this protein in normal functioning of the human body and its association with the various disease processes.

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