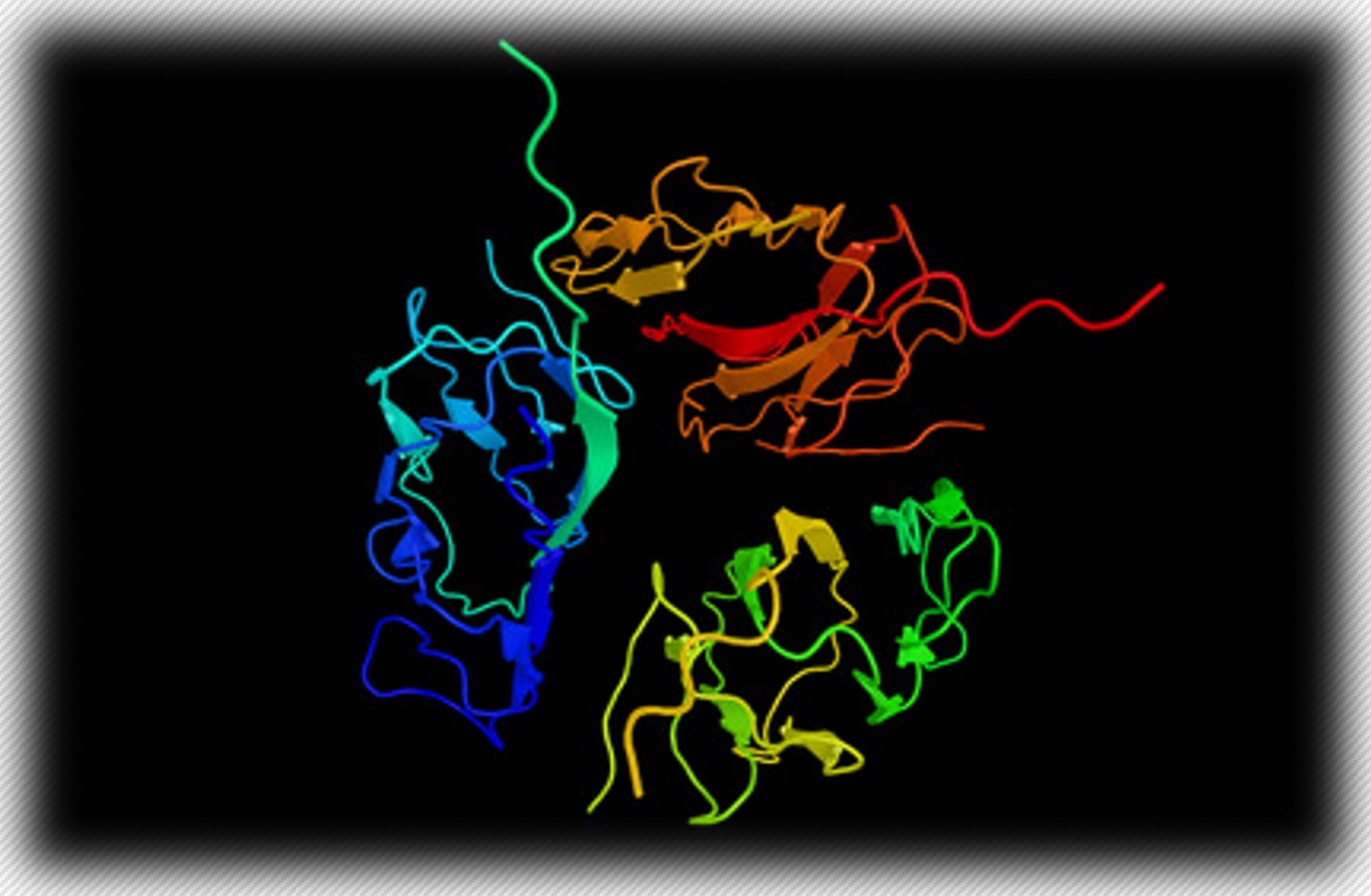
JULY 2023
ISSUE 07

In this issue: ELASTIN

News bulletin of AMBI West Bengal Chapter

The Biochemistry Chronicles



ELASTIN

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Elastin is an important component of the connective tissue of the vertebrate animals. It is highly elastic and present in connective tissue allowing many tissues in the body to resume their shape after stretching or contracting. Elastin helps the skin to return to its original position when it is poked or pinched. It is also an important load-bearing tissue in the bodies of vertebrates and used in places where mechanical energy is required to be stored. Elastin is roughly 1000 times more flexible than collagens It is a very long-lived protein, having half-life of over 78 years in humans.

Biosynthesis of elastin:

Elastin is encoded by the ELN gene present in chromosome no 7 in humans. It is rich in hydrophobic amino acids such as glycine and proline, which form mobile hydrophobic regions bounded by crosslinks between lysine residues. Multiple transcript variants encoding different isoforms have been found for this ELN gene.

The synthesis of tropoelastin begins with the transcription of the ELN gene in the nucleus. In the endoplasmic reticulum, tropoelastin interacts with elastin binding protein (EBP) and folds in structure. After the storage and transport from Golgi, the complex of EBP and tropoelastin is secreted to the cell surface for self-assembly. Then, tropoelastin dissociates from EBP and deposits onto the microfibril scaffold. In the presence of LOX, tropoelastin cross-links and eventually forms mature elastic fibers.

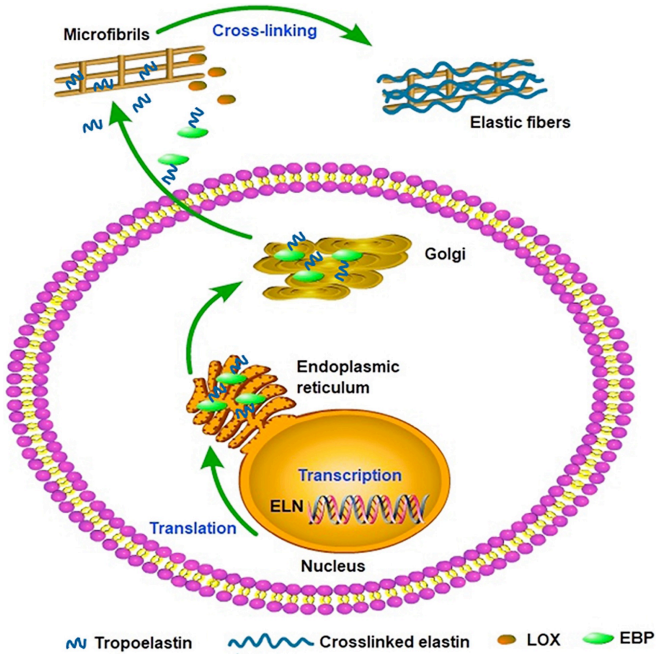

Fig 1: steps of formation of Elastin protein

Tissue distribution:

Elastin serves important function in the arteries as a medium for pressure wave propagation to help blood flow and is particularly abundant in large elastic blood vessels such as the aorta. Elastin is also very important in the lungs, elastic ligaments, elastic cartilage, the skin, and the bladder.

The elastic fibers in a healthy heart are mainly distributed in endocardium, visceral pericardium (epicardium), arterial wall, and cardiomyocytes and interweave with collagen fibers maintaining elastic properties and strength.

Structure of elastin:

Elastin is a structural protein rich in glycine, proline, alanine leucine & valine residues & is generally organized in short repeated sequences of three to nine amino acids that form flexible & highly dynamic structure.

Elastin has been less well defined chemically than collagen. But, unlike collagen, it is extremely difficult to solubilize in intact form. As a consequence, many approaches have been developed for biochemically measuring elastin, resulting in widely variable estimations of elastin content for several tissues and organs.

In human body, elastin is associated with other proteins in connective tissues. Elastic fiber in the body is the mixture of amorphous elastin and fibrous fibrillin. Both components are primarily made of smaller amino acids such as glycine, valine, alanine, and proline. The total elastin ranges from 58 to 75% of the weight of the dry defatted human arteries. Comparison between fresh and digested tissues shows that, at 35% strain, a minimum of 48% of the arterial load is carried by elastin, and a minimum of 43% of the change in stiffness of arterial tissue is due to the change in elastin stiffness.

Tropoelastin precursors:

Elastin is made by linking together many small soluble precursor tropoelastin protein molecules (50-70 kDa), to make the final massive insoluble, durable complex. The unlinked tropoelastin molecules are not normally available in the cell, since they become crosslinked into elastin fibres immediately after their synthesis by the cell, after their export into the extracellular matrix.

Each tropoelastin consists of a string of 36 small domains, each weighing about 2 kDa in a random coil conformation. The protein consists of alternating hydrophobic and hydrophilic domains. The hydrophilic domains contain Lys-Ala (KA) and Lys-Pro (KP) motifs that are involved in crosslinking during the formation of mature elastin. In the KA domains, lysine residues occur as pairs or triplets separated by two or three alanine residues (e.g. AAAKAAKAA) whereas in KP domains the lysine residues are separated mainly by proline residues.

Aggregation & crosslinking:

Tropoelastin aggregates at physiological temperature due to interactions between hydrophobic domains in a process called coacervation. This process is reversible, thermodynamically controlled and does not require protein cleavage. The coacervate is made insoluble by irreversible crosslinking.

Finally, to make mature elastin fibres, the tropoelastin molecules are cross-linked via their lysine residues with desmosine and isodesmosine cross-linking molecules. The enzyme responsible for the crosslinking is lysyl oxidase.

Fibrillin microfibrils usually associate with elastin in most of the connective tissues & contribute to the elastic functions of these tissues acting as a stiff reinforcer of elastin containing tissues. Fibrilin 1 is a major component of microfibrils that form a sheath surrounding the amorphous elastin.

Clinical importance of elastin:

Deletions and mutations of ELN gene are associated with supravalvular aortic stenosis (SVAS) and the autosomal dominant cutis laxa.

Other associated defects in elastin include Marfan syndrome, emphysema caused by α1-antitrypsin deficiency, atherosclerosis, Buschke-Ollendorff syndrome, Menkes syndrome, pseudoxanthoma elasticum, William syndrome etc

Role in atherosclerosis: The altered homeostasis between synthesis and proteolysis of ECM proteins contribute to the development of atherosclerosis. The alteration of elastin amounts, incorrect assembly, elastic fiber modification, and elastin fragments are also associated with atherosclerosis. The decrease in the ratio of elastin and collagen leads to arterial stiffness and arterial dilatation, further negatively affecting the normal function of blood vessels.

Role in myocardial ischemia & reperfusion injury: The mechanisms involved in myocardial ischemia-reperfusion injury include reperfusion triggered oxidative burst, calcium overload, and mitochondrial damage, which together induce cardiomyocyte apoptosis and necrosis leading to irreversible damage. Myocardial tissues on normal condition contain a small number of elastic fibers, which are primarily derived from fibroblasts and smooth muscle cells. Research done in rats shows that fibrosis occurs in the infarcted area after suffering from myocardial ischemia (MI), forming cicatricial tissues, which decrease the elasticity of the ventricular wall and influence heart function. Reactive oxygen species are generally considered as toxic by-products of aerobic metabolism and the main cause of macromolecular damage, and reperfusion is associated with the outbreak of ROS production. The synthetic derivative of elastin, Elastin-Derived Peptide VGVAPG is involved in activating the survival/healing pathway of myocardium after myocardial ischemia.

William Syndrome: it is caused by partial deletion of upto 28 genes on chromosome 7. Signs & symptoms include gradual hearing loss, dental abnormalities, mental retardation, Elfin facies, hypocalcemia & supra valvular aortic stenosis. Defective synthesis of elastin causes abnormal growth of joints (soft & weak) & loose skin

Marfan syndrome: a mutation of fibrilin1 gene causes Marfan syndrome. Signs & symptoms include abnormally long extremities in proportion to the rest of the body, curvature of spine, flat feet & heart defect (aortic aneurysms)

Role in emphysema: alveolar elastic fibers are critical for respiratory structure & function. Elastic fibers are uniquely responsible for the property of passive tissue recoil, which is necessary for expiration & proper ventilation. Destruction of elastin or abnormalities in elastic fiber assembly are major factors in emphysema. In alpha 1 antitrypsin deficiency, there is mutation of AERPINA gene at chromosome 14. There is defect in inhibition of neutrophilic elastase enzyme. So, there is there is degradation of elastin protein in lung alveoli which causes emphysema.

Dermatological manifestations:

Cutis Laxa: can be caused by mutations in several genes. Autosomal dominant cutis laxa is the most common form of disorder caused by ELN gene mutation. Disease is characterized by lax skin, wrinkled, sagging & loss of elasticity. The skin around the face, arms, legs & trunk is most commonly affected. There is hypermobility of the joints because of lax ligaments & tendons.

Elastosis: Elastosis is the buildup of elastin in tissues. It is a form of degenerative disease. There are multiple causes of elastosis, but the most commonly the actinic elastosis of the skin, also known as solar elastosis, which is caused by prolonged and excessive sun exposure, a process known as photoaging. Uncommon causes of skin elastosis include elastosis perforans serpiginosa, perforating calcific elastosis and linear focal elastosis.

Actinic elastosis: Occurs due to the replacement of collagen fibers by elastin in the papillary & reticular dermis.

Elastosis perforans sarpiginosa: degeneration of elastin fibers & formation of trans epidermal perforating canals

Therapeutic applications:

Artificial biomaterial for urological tissue engineering:

As elastin fibers are able to recoil after stretching and the long-term stability of the elastin fibers makes it a desirable protein for dynamic organ tissue engineering. It has been reported that solubilized elastin can not only induce angiogenesis, but also increase elastic fiber synthesis

Tissue engineering of larynx: synthetic elastomers:

Recombinant tropoelastin, solubilized elastin, and elastin-based peptides are mainly used in the assembly of synthetic biodegradable elastomers. These can be converted into fibrous scaffolds or cast into hydrogel.

The Elastin Like Polypeptides are biopolymers with the pentapeptide repeat of amino acids (valine-proline-glycine-Xaa-glycine). A study combining ELPs with hydrogels demonstrated improved vocal fold wound healing
An elastin-mimetic hybrid polymer (EMHP) was recently developed which resembles the structure of tropoelastin with the elastic quality of mature elastin. In vitro, primary porcine vocal fold fibroblasts grew throughout 3 days of culture and assumed normal cell morphology.

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