Tissues, Pathology, and Diagnostic Microscopy

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Tissue elasticity: from tissues to single molecules back to tissues

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Soft connective tissues are comprised of a three-dimensional network made of a variety of proteins, glycoproteins and glycosaminoglycans that take part and contribute to strength as well as to plasticity and deformability of the tissue. Amount and ratio of different constituents, protein and cell interactions and supramolecular organization of matrix components are strictly dependent on the capacity of tissues to retain their original shape when relaxed after stretching. Within this context, elastin, the major component of elastic fibers, is secreted as a soluble monomer, undergoes few post-translational modifications and is organized into a polymer that forms lamellae, fibers or hive-like structures according to organ's requirements in order to better provide the recoil properties and the resilience essential to accomplish repetitive distension and physical stress typical for instance of arteries, lung, bladder and skin. Changes of these characteristics, as in aging and in the course of several genetic and acquired disorders, may have therefore dramatic consequences on the structural and functional performance of tissues/organs.

Since the largest amount of elastin is produced during the fetal and neonatal period with a negligible turnover in the following years, the elastin produced during body growth and development has to be maintained for lifespan and any proteolytic damage is essentially irreparable. Moreover, the age-dependent increased stiffness of tissues results from an increase in elastin fragmentation as well as from abnormal deposition of collagens, calcium and lipids, in addition to non-enzymatic post-translational modifications of matrix proteins such as carbamylation and glycoxydation.

During atherosclerosis and vascular aging, the extracellular environment and elastin in particular are importantly modified due to the local inflammatory context. Interestingly, proteolytic enzimes, as elastases and endopeptidases, are responsible for elastic fragmentations thus affecting the structural properties of tissue, but also generating an incredible amount of the so-called elastin-derived peptides (EDP) that can modulate the physiology of cells such as fibroblasts, smooth muscle cells, endothelial cells, monocytes/macrophages and lymphocytes. These active peptides are also known as elastokines since they belong to the matrikine family and trigger a plethora of biological activities: some beneficial to heart as protection against ischemia/reperfusion injury or to tissue repair, whereas others are deleterious as in aortic abdominal aneurysms, calcification of vessel walls, formation of hyperplasic neointima and in the progression of cancer growth and invasion.

The organization of the elastin molecule into alternate hydrophobic and hydrophilic domains stimulated studies tending to elucidate the specific role of domains implicated in the assembly of molecules into fibers or in the interactions with cells or with other extracellular constituents. Attention has been also paid to the conformation characteristics of domains in order to explain the elastic behaviour in water of the whole molecule. It is worth mentioning in fact that peptides with amino acid sequences corresponding to the various tropoelastin domains exhibit peculiar chemical physical characteristics and form, depending on environmental conditions, aggregates with distinctive supramolecular organization and biological properties. Exploring these characteristics has a fundamental impact for a better understanding of a disease-related pathomechanisms but also for an improved formulation of nano-biocomposites to be used as implants into living beings. One of the main concerns as far as the use of biomaterials should be to check for the activation of the inflammatory process and of the immune response. These processes may in fact alter the implant and would favour its retention or its rejection.

The inflammatory process is in fact characterised by recruitment and activation of macrophages, production of molecules with proteolytic activities and of cytokines with stimulatory effects on macrophages themselves, lymphocytes and fibroblasts. Moreover, proteolysis may favour elastin breakdown leading to the formation of elastin fragments, which, in turn, may have immuno-modulatory effects.

In vitro studies have demonstrated that even very simple elastin-derived peptides exhibit rather specific biological activities. Consistently, investigations on the chemotactic activity of peptides derived

from the coding sequence of exon 26A of the elastin gene (i.e. an exon that is not expressed in humans in normal conditions, whereas it is expressed in some pathological processes, such as in hypertension) revealed that these peptides exhibit a conformation-dependent chemotactic activity for monocytes/macrophages, indicating that the biological activity of elastin-derived peptides mostly depends on their structural organization.

As a whole, elastin-derived peptides have been shown to elicit a series of cellular responses, from elastase release, to free radical production and LDL oxidation. However, not all elastin peptides would seem to stimulate inflammatory cells in the same way, being some peptides more active than others in the production of free radicals, or in the elastase release or in the intracellular free calcium metabolism.

Furthermore, recent studies have also disclosed the amyloidogenic properties of several elastin-derived peptides, further highlighting the role of the extracellular matrix in many pathologic conditions and the importance to investigate each matrix constituents at molecular and supramolecular levels to get further insights into tissue structural and functional properties.

Within this context elastin and elastin peptides can be regarded as a paradigm to explore the complexity of the mechanisms responsible and/or contributing to tissue elasticity.

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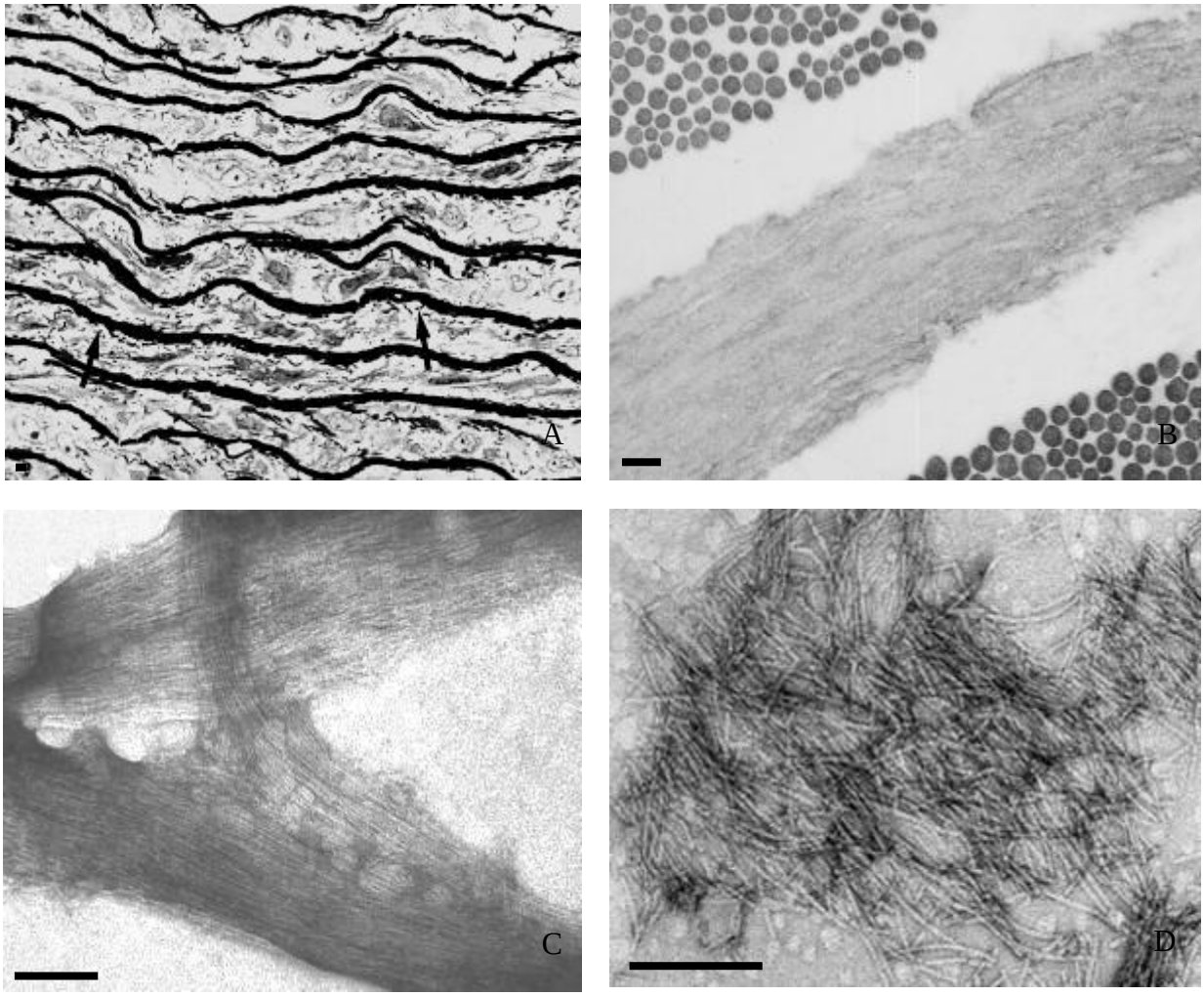

Figure 1. Light microscopy showing the elastic component organized as lamellae (arrows) between layers of vascular smooth muscle cells (A). Transmission electron microscopy of a typical dermal elastic fiber in a skin biopsy (B), of in vitro coacervated tropoelastin (C) and of isolated and purified elastin peptides (D). Bar 1 □m.