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The function of elastic fibers in the arteries: Beyond elasticity

La fonction des fibres élastiques artérielles : au-delà de l'élasticité

M. Lannoy, S. Slove, M.-P. Jacob *

Inserm U1148, université Paris 7, hôpital Bichat-Claude-Bernard, 46, rue Henri-Huchard, 75877 Paris cedex 18, France

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ABSTRACT

The main components of elastic fibers, elastin and fibrillin-containing microfibrils play a structural and mechanical role in the arteries and their essential function is to provide elasticity and resilience to the tissues. However, through control of the quiescent contractile phenotype of arterial smooth muscle cells, elastin also acts as an autocrine factor and, *via* the binding of 'latent transforming growth factor (TGF)-β binding protein (LTBP) – latency-associated peptide (LAP) – TGF-β' complexes, fibrillins regulate the activation and availability of TGF-βs. These recent discoveries are detailed in this review.

RÉSUMÉ

Les principales composantes des fibres élastiques, l'élastine et les microfibrilles contenant les fibrillines, jouent un rôle structural et mécanique dans l'aorte et les artères et leur fonction essentielle est de fournir l'élasticité aux tissus. Toutefois, grâce au contrôle du phénotype contractile et quiescent des cellules musculaires lisses artérielles, l'élastine agit également comme un facteur autocrine et, par l'intermédiaire de la liaison des complexes « latent transforming growth factor (TGF)-β binding protein (LTBP) – latency-associated peptide (LAP) – TGF-β », les fibrillines régulent l'activation et la biodisponibilité des TGF-β. Ces découvertes récentes sont détaillées dans cette revue.

1. Introduction

Elastic fibers, composed of elastin and microfibrillar glycoproteins, are present in tissues which require the functional property of elasticity and recoil; they are detected in blood vessels, heart valves, lungs, skin, intervertebral discs and ear elastic cartilage [1–4]. With the exception of bovine *ligamentum nuchae*, which contains 80% (% dry weight) of elastin, the elastin content of tissues varies from 40% in the ascending thoracic aorta to few percent in the skin.

The spatial organization of elastic fibers is highly variable in the extracellular matrix of the different tissues. In arteries and veins, elastic fibers are organized as thick lamellae whereas three types of fibers, oxytalan, elaunin and elastic fibers are observable in the skin. Thin interlamellar elastic fibers are also observed in blood vessels.

The creation of elastin knock-out mice has revealed that, besides conferring elasticity, elastin and elastic fibers have other functions: elastin is required for arterial morphogenesis. Since this discovery in 1998, the mechanisms linking elastin synthesis to arterial morphogenesis have been deciphered.

During the synthesis of microfibrillar glycoproteins and the formation of microfibrils, latent transforming growth factor (TGF)-β binding proteins (LTBPs) interact with fibrillins. LTBPs subsequently localize to fibrillin-rich microfibrils and microfibrils control the activation and bioavailability of TGF-βs.

In this review, these properties of elastic fiber components are detailed.

* Corresponding author. Tel.: +33 1 40 25 86 17; fax: +33 1 40 25 86 02.
E-mail address: marie-paule.jacob-lenet@inserm.fr (M.-P. Jacob).

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2. Elastin and elastic fibers in the arteries

Elastic fibers can be observed in detail using various methodologies (histology, confocal microscopy, transmission or scanning electron microscopy, multiphoton laser scanning microscopy), in whole tissue or after purification [5–7] (Fig. 1). In the arteries, the elastic fibers are mainly organized as concentric, fenestrated lamellar sheets, linked to each together by interlamellar elastic fibers [8]. The elastic lamellae are synthesized by the smooth muscle cells in the media of arteries [9–11]. The number of elastic lamellae and the quantity of elastin decreases in the aorta from the heart to the iliac bifurcation [12]. In the muscular arteries, only the internal and external elastic lamellae are clearly discernable; within the media, only a few discontinuous elastic lamellae are present (Fig. 1).

In the mature elastic arteries, each monolayer of smooth muscle cells are separated by one elastic lamella. The regular layering of smooth muscle cells between elastic lamellae has led to the definition of the lamellar unit [13]. Between elastic lamellae, smooth muscle cells are surrounded by collagen fibers, proteoglycans, such as versican, and glycoproteins [6].

3. The formation of arterial elastic fibers

At the molecular level, elastic fibers are composed of microfibrillar glycoproteins surrounding and embedded in an amorphous core of elastin [1,5,14,15]. Microfibrillar glycoproteins are mainly fibrillins and microfibrillar-associated glycoproteins [1,3]. Fibrillin-containing microfibrils are first synthesized and tropoelastin molecules, complexed with the three subunits of the elastin receptor, are deposited on this protein scaffold. Tropoelastin molecules coalesce in the extracellular space and are linked one to another during the cross-linking process [1,2]. This cross-linking process begins with the oxidative deamination of lysine residues. One lysyl oxidase enzyme catalyzes this first step, which produces a very reactive aldehyde function. The association of four lysine residues leads to the formation of desmosine or isodesmosine, specific cross-links of elastin [1].

After this cross-linking process, elastin becomes insoluble.

Mutations in one of the three subunits of the elastin receptor, which act as a chaperone protein, demonstrate further its role in the elastin synthesis [16,17].

The suppression of the lysyl oxidase isoform LOX is more detrimental to elastic and collagen fiber formation than the suppression of LOXL-1 [18–21].

In the aorta, elastin synthesis begins at mid-gestation when the blood pressure rises above a few millimeters of Hg [1,2]. The number of elastic lamellae is defined during prenatal development [22,23]. After birth, each elastic lamella grows uniformly as the arterial length, diameter and wall thickness increase during growth [14,15]. During the growing phase, elastin is also deposited around the borders of the fenestrations.

By the analysis of mice hemizygous for the elastin gene (*Eln+/-*) which, paradoxically, have an increased number of elastic lamellae in the aorta, we have learnt that the reduction in elastin synthesis induces a structural adaptation of the aorta during foetal development [22–26]. In the proximal thoracic aorta, the number of elastic lamellae and smooth muscle cell layers is established at 8 by day 18 of embryonic development and will not change during future development in wild-type mice [23]. However, it increases from 8 to 11 and the aorta thickens during the last three days of prenatal development in *Eln+/-* mice and increases even more in *Eln-/-* mice [23–26]. The increased proliferation of smooth muscle cells of *Eln-/-* mice will lead to occlusion of the main arteries and, consequently, to death of the mice, three days after birth [26]. The discovery of the phenotype of *Eln-/-* mice has led to the conclusion that, besides the well-known mechanical property of elasticity, elastin is also an essential determinant of arterial morphogenesis [26].

There are three isoforms of fibrillin [27]. Fibrillin-2 is mainly expressed during prenatal development, is still detectable one day after birth (in the mouse and the rat) and becomes almost undetectable thereafter [2,28–30]. Synthesis of fibrillin-1 is variable during prenatal and post-natal development but is detected throughout life [2,28–30]. Fibrillin-2-/- (*Fbn2-/-*) mice have no arterial defects whereas *Fbn1-/-* mice die soon after birth

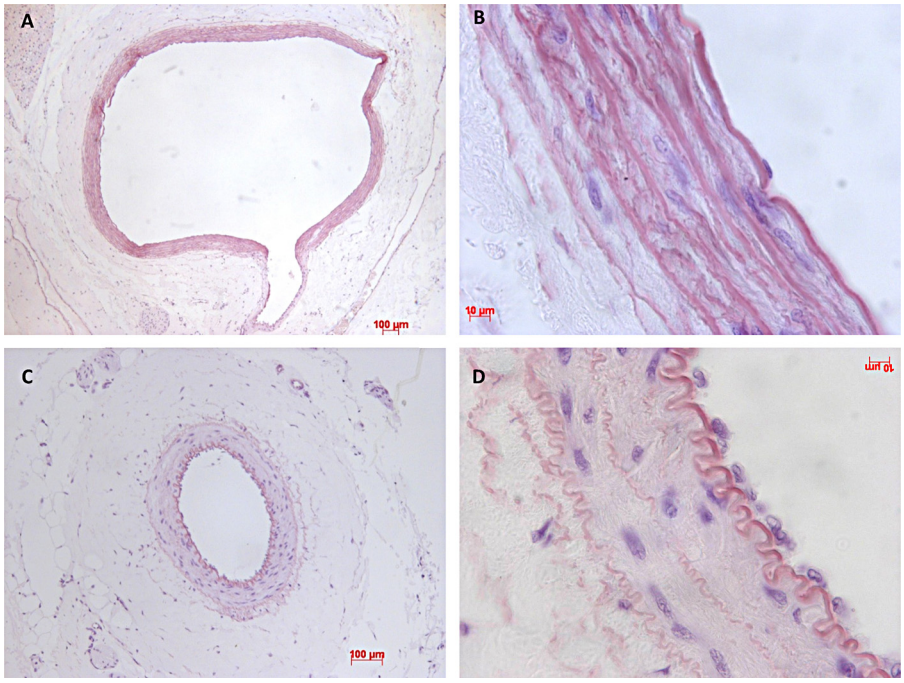

Fig. 1. Transversal sections of a rat subrenal abdominal aorta (A, B) and a rat femoral artery (C, D), stained with orcein and hematoxilin. Bar = 100 µm (A, C) or 10 µm (B, D).