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Signaling pathways in elastic tissues

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ABSTRACT

For many years elastin was considered as the matrix component structurally required to provide tissue elasticity. However, the expanded knowledge on the regulation of connective tissue homeostasis has revealed that elastic fibers also represent a source of elastokines and are the target of a number of signaling pathways mainly involving the TGF-β/BMP axis. A better understanding of these complex regulatory networks may pave the way for targeted therapeutic strategies in a number of genetic as well as acquired diseases and for the development of new functionalized biomaterials.

Elastin is present in all vertebrates and consists of a three-dimensional network of fibers or lamellae spread through the extracellular matrix of many connective tissues, being particularly abundant in elastic vessels, ligaments, lungs and skin [1]. It is one of the longest-lived protein in humans and metabolically stable over a lifetime [2].

Elastic fibers are principally composed of a crosslinked elastin core deposited on a scaffold of fibrillin-rich microfibrils which requires, for its initial formation, the assembly of fibronectin molecules [3]. To be noted is that the soluble precursor tropoelastin is deposited onto microfibrils with the help of many other matrix components such as proteoglycans [4,5], fibulins 4 and 5 [6], as well as latent TGF-β binding protein-4 [7]. Thereafter, lysyl oxidase and lysyl oxidase-like 1 enzymes promote the crosslinking of newly formed elastic fibers in order to guarantee the long-lasting mechanical stability of the fibers [8]. This remarkable property, together with its elasticity, makes elastin a valuable matrix constituent to be used as a tunable biomaterial for a variety of tissue engineering applications [9–11].

In vivo, elastin synthesis is developmentally and functionally regulated: tropoelastin appears during the embryonic phase (i.e. vessels formation) up to the last period of gestation (i.e. skin and lung growth) and increases around and immediately after birth [12].

During life, degradative processes seem to outweigh synthesis and the altered ratio with other components, as collagen, is responsible for changes in tissue biomechanical properties as clearly evident in the age-related modifications of the vascular system where reduced vessel extension and arterial pulse wave reflections may contribute to increase pulse pressure, thus redisposing to heart failure [13].

Moreover, aged elastin is degraded and other molecules progressively substitute for elastin within the fiber, thus dramatically affecting tissue elasticity and contributing to the maintenance of a chronic inflammatory state, i.e. inflamm-aging [14]. Inflammatory cells and alveolar macrophages, for instance, are mainly responsible for degradative processes in lungs, whereas lipid deposition, inflammatory reactions and elastase release are more likely involved in blood vessels.

Interestingly, it has been demonstrated that elastic fiber degradation can release elastin fragments named elastokines due to their cytokine-like signaling properties [15], as they exhibit potent chemotactic activities for leukocytes, stimulate fibroblast and smooth muscle cell proliferation and display proangiogenic activity, thus sustaining the use of these peptides, as substitutes of the whole molecule, for bioengineering applications [16], including the generation of bio-inspired materials based on the repetitive sequence XGGZG (X,Z = V,L or A) forming amyloid-like nanostructures [17,18]. A typical elastokine is the VGVAPG peptide, found in the exon 24-encoding sequence [19], but also longer peptides were shown to be bioactive [20] and the analysis of fragments generated by atherosclerosis-related elastases brought into light new bioactive GXXPG-related peptides as GVYPG, GFGPG and GVLPG [21]. For biological activity of elastin peptides, binding to specific receptors is needed. These include galectin-3 [22] and $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins [23–25], but mainly relies on the elastin receptor complex [26,27]. This complex comprises three subunits: the elastin binding protein, the protective protein/cathepsin A (PPCA) and the membrane bound neuramidase-1. The elastin binding protein binds elastin-derived peptides, but also has a binding site for a galactosugar. Upon binding of a galactosugar, the elastin binding protein releases from the complex preventing further biological effects of elastin-derived peptides. PPCA exhibits enzymatic activity that is needed for correct elastic fiber formation [28]. Neuraminidase-1 exhibits sialidase activity needed for signal transduction. It may desialylate various receptors, as was demonstrated for e.g. platelet-derived growth factor receptor, insulin-like growth factor receptor 1 [29] and recently CD36 [30]. Due to the general desialylation activity of Neuraminidase-1,

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effects on other membrane-bound receptors are anticipated. Intracellularly, elastin-derived peptides are able to activate multiple signaling pathways, including protein kinase C (PKC), phosphoinositide 3-kinase (PI3K) and phospholipase Cg (PLCγ) [27] and to drive tumor development by regulating cell proliferation, invasion, survival, angiogenesis, and matrix metalloproteinase expression or to regulate diabetes outcome and thrombosis [26].

Recent investigations have demonstrated that loss of fibrillin microfibrils is the hallmark of early photodamage since *in vitro* UVB irradiation induces reactive oxygen species-driven structural changes to both fibrillin-microfibrils and fibronectin, thus enhancing protein damage [31]. Interestingly, fibrillin-microfibrils are relatively resistant to proteolysis by matrix metalloproteases (MMP) as MMPs −1, −3, −7 and − 9, but, as it was underlined in the present issue, MMPs may exert also a positive role selectively removing damaged microfibril assemblies [31]. At the same time, fibrillin fragments containing an RGD site can upregulate MMP-1 and MMP-3 expression [32] and mutations in fibrillin peptides associated with Marfan syndrome are responsible for increased susceptibility of elastic tissues to MMP degradation [33]. This finding supports the concept that photodynamic production of ROS represents a key mechanism for non-enzymatic protein damage and MMP proteolysis especially effective on already damaged microfibrils [31].

As mentioned, elastic fibers undergo irreversible alterations during aging and in several pathological conditions such as in rare genetic disorders [34], where elastin is poorly synthesized (i.e. Cutis laxa), scarcely polymerized (i.e. Menkes) or progressively mineralized (i.e. Pseudoxanthoma elasticum). The expanded knowledge on elastin synthesis and deposition [35] and a better understanding of the complex composition of elastic fibers [36] is disclosing a number of pathogenic signaling pathways, thus opening new therapeutic perspectives. For instance, absence or reduced expression of fibulin-4 negatively affects the recruitment of lysyl oxidase, thus inhibiting tropoelastin to properly crosslink [6]. Consistently, mutations in fibulin-4 have been associated with a form of cutis laxa, an autosomal recessive disorder characterized by loose skin, aneurysms and vessel structural abnormalities [37]. In the light of data obtained in vascular smooth muscle cells with reduced or absent fibulin-4 expression and increased or unaltered TGF-β signaling [38], it has been suggested in the present issue that, in addition to TGF-β signaling, cytoskeleton structure and dynamic organization [39] can play a pathogenic role in the development of aneurysms. In particular, increased TGF-β signaling can exert a protective role in early stages of the disease, whereas it may have a damaging effect in later stages of the disorder and, as proposed by the authors, cytoskeleton dynamics could represent a causative factor contributing to aortic aneurysmal disease.

In vitro, it has been shown that elastin gene expression can be stimulated in smooth muscle cells if these cells are periodically stretched, suggesting that mechanical forces from the extracellular matrix, possibly transmitted through the integrin system to the cytoskeleton and to the nucleus, may exert additional regulatory function [40]. Among exogenous factors known to modulate elastin deposition, vitamin C has been demonstrated to negatively affect elastin gene expression and tropoelastin synthesis by altering mRNA stability and post-translational mechanisms [41], whereas cytokines such as TGF-β [42] and drugs as minoxidil, an ATP-dependent K^+ channel opener [43], can stimulate elastin deposition by a complex interplay of signaling pathways. Minoxidil has been shown to stimulate elastin mRNA expression *in vitro* in skin fibroblasts [44] and smooth muscle cells conceivably through a Ca^{2+}- ERK (extracellular signal-regulated kinases)–dependent pathway [45]. *In vivo*, minoxidil increased the elastin content in arteries of young adult hypertensive rats [46] and induced the differential expression of 127 extracellular matrix related genes in $Eln^{+/-}$ mice [47]. In the present issue, a study demonstrates that minoxidil not only promotes the formation of newly synthesized elastic fibers, but also preserves elastic lamellae integrity [48], thus significantly improving arterial biomechanical properties. The authors state that minoxidil may counteract the consequences of arterial aging by acting as an “anti-arterial-aging” agent due to reducing elastase activities, AGE-dependent cross-linking and possibly inflamm-aging. Interestingly, the effects were more prominent in female mice, suggesting that elastin regulation can also be influenced by gender, possibly through hormone-driven mechanisms [49].

Although the elastogenic capabilities of TGF-β have been demonstrated since the late eighties [50], the signaling pathways modulated by the cytokine have been explored into depth more recently, including its involvement in the pathogenesis of a number of diseases mainly affecting bone, lungs and the cardiovascular system [51].

TGF-β is synthesized in form of a precursor protein that is proteolytically processed and secreted by cells in an inactive form. Latent-TGF-β (LTBP) is bound to fibrillin-1 and this complex constitutes a reservoir of the cytokine that can be rapidly released in response to specific stimuli. TGF-β activates signaling pathways through type I and type II Ser/Thr kinase receptors and intracellular SMAD effectors [52]. Within this context, bone morphogenetic protein (BMP) can play a major regulatory role, since altered TGF-β/BMP signaling pathways have been linked to a variety of clinical conditions, i.e. skeletal and extra-skeletal abnormalities, autoimmune and cardiovascular diseases and cancer [53].

Investigations focusing on the effects of BMP-induced signaling in bone dynamics revealed that these pathways are spatiotemporally modulated by the transcription factor RUNX2 as well as by MAPK, Wnt, Hedgehog (Hh), Notch and Akt/mTOR [52]. Moreover, TGF-β and BMP signaling can contribute to diseases characterized by progressive elastin calcification [54], as in Pseudoxanthoma elasticum (PXE) and PXE-like disorders, rare inherited diseases due to mutations in either ABCC6 [55], GGCX [56] and/or ENPP1 [57] genes. Interestingly, TGF-β can modulate ABCC6 promoter activity [58] and, as suggested in the present issue, ABCC6 deficiency may be related to the increased TGF-β expression observed in PXE cells and possibly to the upregulation of the osteogenic BMP2 - SMAD1/5/8 - RUNX2 and ALP pathways [59]. Together with the increased activity in the MSX2-Wnt signaling, these changes promote the osteogenic transdifferentiation of PXE fibroblasts, favoring increased ANKH expression and PPi release through activation of ERK1/2 and PKCα pathways [59].

In line with these findings is the observation, also reported in the present issue, that, in beta thalassemic patients affected by ectopic calcification, a modified microfibrillar scaffold can contribute to the activation of pSMAD2/3 and pSMAD1/5/8 signaling pathways, further supporting the role of TGF-β/BMP pathways in elastic fiber calcification [60]. Furthermore, data from whole exome sequencing in these patients revealed changes in mitochondrial metabolic pathways, in agreement with previous data indicating that a persistent chronic oxidative stress [61] can further influence extracellular matrix homeostasis [62]. In particular, the presence of rare sequence variants in the solute carrier family 25 member 5 (SLC25A5) gene is suggestive of the role of this gene as a key factor linking mitochondrial metabolism, ADP/ATP ratio and oxidative stress, thus activating pro-osteogenic factors that lead to elastic fiber calcification [60].

In conclusion, the progressively growing literature in the area of matrix biology has largely expanded the knowledge on elastic tissues, nevertheless an urgent demand remains for studies further addressing the importance of elastin and of elastic fiber components in terms of developmental requirements, structural and mechanical properties, signaling pathways and the role of the elastin receptor complex in physiologic as well as in pathologic context. Researchers are sincerely encouraged to share their expertise and most recent results in conferences specifically dedicated to “Elastin and elastic tissues” every year, alternately, at the Gordon Research Conferences and at the European Elastin Meeting.

Acknowledgments and Congress annotations

Authors are grateful to all participants to the 10th European Elastin Meeting held from 14 to 16 June 2018 in Nijmegen, the Netherlands and in particular to those who agreed to contribute to building up this special issue of Cellular Signaling. The conference not only included cellular signaling as a main topic, but also development, pathology, (supra)molecular structure, elastic fiber assembly, and biomaterials & regenerative medicine. As honorary invited speaker, Kirk Hansen (University of Colorado) gave insight in the analytical characterization of extracellular matrix especially focusing on elastin using mass spectrometry, thus emphasizing the importance of matrix interactions and metabolomic studies for better understanding the complexity of the extracellular milieu in governing cellular response and behavior. The innovative contribution of young researchers to the elastin field was acknowledged by an independent jury who selected the recipients of two early-stage researcher awards. The oral presentation prize was handed out to Joyce Burger (Erasmus Medical Center, Rotterdam, The Netherlands) for her presentation “Fibulin-4 deficiency differentially affects TFG-β signaling as well as cytoskeleton structure and dynamics” that has been incorporated in an extended paper published in this special issue [39]. The poster prize was awarded to Lars Damen (Radboud university medical center, Nijmegen, the Netherlands) for his poster entitled “Development of tools to study the sulfation pattern of heparan sulfate involved in elastic fiber biology”, focusing on the development of single chain variable fragment antibodies to target several sulfation patterns in the glycosaminoglycan heparan sulfate and to study the interactions of heparan sulfate in (patho)physiological processes, including elastic fiber biology.

The next European Elastin Meeting will take place from 4 to 6 June 2020 and will be organized by BIOFORGE, Group for Advanced Materials and Nanobiotechnology of the University of Valladolid, Spain.

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