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Cellular interactions with elastin

Interactions cellulaires avec élastine

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Abstract

Elastin is a key structural component of the extracellular matrix. Tropoelastin is the soluble precursor of elastin. In addition to providing elastic recoil to various tissues such as the aorta and lung, elastin, tropoelastin and elastin degradation products are able to influence cell function and promote cellular responses. These responses include chemotaxis, proliferation and cell adhesion. The interaction of elastin products with cells has been attributed to the elastin receptor. However, additional cell-surface receptors have also been identified. These include G protein-coupled receptors and integrins. The potential roles of these receptors in cell–elastin interactions, with particular focus on elastin formation are discussed.

Résumé

L'élastine est un composant essentiel de la matrice extracellulaire. La tropoélastine est le précurseur soluble de l'élastine. Outre leur rôle dans l'élasticité des tissus comme l'aorte et les poumons, la tropoélastine, l'élastine et ses produits de dégradation agissent sur les cellules et déclenchent des réponses cellulaires. Ces réponses comprennent le chimiotactisme, la prolifération et l'adhésion cellulaires. L'interaction des dérivés de l'élastine avec les cellules a été attribuée au récepteur de l'élastine. Cependant, d'autres récepteurs cellulaires ont aussi été identifiés. Ceux-ci comprennent des récepteurs couples à des protéines G et des intégrines. Le rôle potentiel de ces récepteurs dans l'interaction cellules–élastine est discuté et en particulier dans la formation de l'élastine.

Keywords: Elastin; Tropoelastin; Biosynthesis; Cell–elastin; Interactions; Integrins

Mots clés : Elastine ; Tropoélastine ; Biosynthèse ; Interactions cellules–élastine ; Intégrines

1. Introduction

Elastin, the major component of elastic fibers, represents a significant structural component of the vertebrate extracellular matrix (ECM). The principal role of elastin is to provide the elastic recoil properties and resilience essential to proper function of tissues that are subject to repetitive distension and physical stress. These include the aorta [117], lung [81], bladder [19] and skin [37]. Elastin is essential for proper arteriogenesis and distal airway development, as shown in knockout mouse models [74,124]. Compromised elasticity due to degradative changes contributes significantly to ageing of connective tissues, in the development of aortic aneurysms and emphysema, and in degenerative changes in sun-damaged skin [123].

Elastin is a chemically inert, highly insoluble polymer composed of covalently cross-linked molecules of its precursor or 'building block', tropoelastin, a soluble, non-glycosylated and highly hydrophobic protein [104,112]. Tropoelastin expression and subsequent elastin synthesis typically occurs in fibroblasts [83], vascular smooth muscle cells (VSMC)

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[97], endothelial cells [15], and chondrocytes [93]. Expression of the elastin gene begins around mid-gestation and continues at a peak rate through to the early stages of neonatal development in most mammalian tissues [20,91]. Expression under normal conditions is almost completely repressed by 10 years of age [19,22]. Elevated levels of elastin synthesis have been observed following injury [35,110,116] and as a consequence of pathogenic conditions [84,108,118]) such as aortic restenosis, hypertension and proteolytic lung injury, which have been modelled in animals [4,66,73]. Elastin synthesis may also be affected by elastase degradation of the ECM, an important factor in the progression of diseases such as atherosclerosis [126]. This was observed in neonatal rat aortic smooth muscle cells, where a decline in elastin synthesis was noted around the post-translational stage [127]. However, in a separate study, elastase treatment of certain cell cultures resulted in increased levels of tropoelastin mRNA and protein [30].

2. Primary structure of tropoelastin

One of the major characteristics of the primary structure of tropoelastin is the presence of alternating hydrophobic and hydrophilic regions or domains, each encoded by separate exons [60]. The hydrophilic regions are alanine and lysine rich, and are the targets for lysyl oxidase for subsequent cross-linking [31,101]. The hydrophobic domains, which are rich in repeated motifs containing proline, valine and glycine [121], interact via hydrophobic interactions, and are thought to be responsible for the elastic properties of elastin [75,119]. In addition, many of these regions are thought to behave as specific cell recognition sequences [5,45,107]. The sequence of tropoelastin is highly conserved in mammals at the nucleotide and amino acid levels [61]. In general, the hydrophobic regions are less well conserved than are the hydrophilic domains in both size and composition, though the overall molecular function of tropoelastin is apparently not compromised by variation in the hydrophobic domains [93].

Multiple isoforms of tropoelastin have been identified and characterised in chick aorta and lung [28,29], as well as bovine and ovine nuchal ligaments [18,129]. The human aorta displays the potential for at least seven possible isoforms [60]. These isoforms are the products of alternate splicing of the primary transcript of tropoelastin [60,61,91,129]. At least 10 bovine and six human exons are alternately spliced individually or with adjacent or distant exons in a cassette-like fashion, including 22, 23, 24, 26, 32 and 33 [2,27,61,132]. In addition, alternate splicing may arise from alternate donor or acceptor site usage, resulting in the exclusion of parts of exons, such as the deletion of exon 26A. The exon for domain 26A is rarely expressed, having been detected mainly only in pathological conditions such as pulmonary hypertension [76] and terminally differentiated keratinocytes [53]. The functional significance of these various isoforms is not entirely clear, although it has been proposed that modulation of the amino acid sequence of tropoelastin by alternate splicing may influence the interaction of elastic fibres with other proteins and cells [92]. There is evidence that expression of the various splice forms appears to be developmentally regulated [91,128].

The C-terminus of human tropoelastin, which corresponds to domain 36, contains amino acid sequences that are unique to the protein, including two conserved closely-spaced cysteine residues. These residues are linked by an intramolecular disulphide bond, creating a basic, positively charged tetrapeptide loop [9,13,129]. Domain 36 is highly conserved across species and is not subject to alternate splicing, suggesting an important function for this region of tropoelastin. Evidence suggests that truncated forms of tropoelastin missing the C-terminus are less efficiently incorporated into elastin [10,49,55], suggesting that it plays an essential role in elastic fibre assembly. It was also proposed to mediate intracellular transport of newly synthesised tropoelastin to the cell-surface, though in vitro studies failed to support hypothesis [38]. In addition, the tetrapeptide loop of domain 36 was proposed to be a binding site for microfibrillar proteins, such as MAGP-1 [10]. Microfibrillar proteins form an integral part of the mature elastic fibre. During development, microfibrils are deposited into the extracellular space in close association with the plasma membrane prior to the production of elastin, and behave as a scaffold for elastin deposition [71,102]. Specific interactions of tropoelastin with microfibrillar proteins, most likely via the C-terminal domains of tropoelastin, are thought to help align the cross-linking domains of tropoelastin monomers in order for covalent cross-linking to occur [82].

The necessity of the C-terminal domains of tropoelastin in elastogenesis is emphasised by pathological conditions involving mutations of the elastin gene. Cutis laxa is a rare congenital disorder whose hallmark is defective elastic fibre formation, resulting in fragmented elastic fibres, diminished in number, in the skin [69,109]. The result is loose, hyperextensible skin with decreased resilience and elasticity. Along with skin defects, pulmonary and cardiovascular function is compromised [133]. Cutis laxa involving the elastin gene is an inherited autosomal dominant disorder. Elastin mutations result in the production of stable, but abnormal tropoelastin, which may be incorporated abnormally during elastogenesis [115]. Two frameshift mutations, occurring in exon 30 of the elastin gene, have been identified [133]. These point deletions lead to the loss of the two conserved cysteine residues in domain 36, which create the intramolecular disulphide bridge. Domain 30 is also thought to play a significant role in tropoelastin deposition in the process of elastic fibre synthesis [70]. Autosomal dominant cutis laxa associated with point deletions in exons 32 and 33 have also been identified [100,115]. If the C-terminal region is able to bind microfibrillar proteins such as MAGP-1 or other unidentified proteins [9], it would be expected that the loss of this region could also contribute to impaired elastic fibre formation such as in the development of the ductus arteriosus [49].