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Review

Vascular wall extracellular matrix proteins and vascular diseases

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ABSTRACT

Extracellular matrix proteins form the basic structure of blood vessels. Along with providing basic structural support to blood vessels, matrix proteins interact with different sets of vascular cells via cell surface integrin or non-integrin receptors. Such interactions induce vascular cell de novo synthesis of new matrix proteins during blood vessel development or remodeling. Under pathological conditions, vascular matrix proteins undergo proteolytic processing, yielding bioactive fragments to influence vascular wall matrix remodeling. Vascular cells also produce alternatively spliced variants that induce vascular cell production of different matrix proteins to interrupt matrix homeostasis, leading to increased blood vessel stiffness; vascular cell migration, proliferation, or death; or vascular wall leakage and rupture. Destruction of vascular matrix proteins leads to vascular cell or blood-borne leukocyte accumulation, proliferation, and neointima formation within the vascular wall; blood vessels prone to uncontrolled enlargement during blood flow diastole; tortuous vein development; and neovascularization from existing pathological tissue microvessels. Here we summarize discoveries related to blood vessel matrix proteins within the past decade from basic and clinical studies in humans and animals — from expression to cross-linking, assembly, and degradation under physiological and vascular pathological conditions, including atherosclerosis, aortic aneurysms, varicose veins, and hypertension.

1. Introduction

Blood vessels deliver oxygen and nutrients to body tissues. The major constituent of the vessel wall is the extracellular matrix (ECM), collectively known as stroma or matrix. In arteries or veins, the ECM constitutes more than half of the wall mass and contains mainly collagens and elastin. Other vascular wall constituents include fibronectin, microbifrils (mainly fibrillins), abundant amorphous or soluble proteoglycans, and leucine-rich glycoproteins. The normal blood vessel wall contains several functionally distinct types of vascular matrices, including subendothelial basement membrane, intima, media, adventitia, and interstitial matrix. Each of these vessel sections contains different types of cells and matrix proteins.

1.1. Vascular wall ECM components

All vessel lumens are lined with endothelial cells (ECs) that are anchored on an underlying basement membrane, a thin sheet-like structure containing mainly laminin, type IV collagen, nidogen, perlecan, type XV and type XVIII collagens, fibronectin, heparin sulfate proteoglycan perlecan, and other macromolecules [1–3]. At least 20 ECM proteins have been identified from basement membrane preparations. Most of these proteins, if not all, have tissue-specific functions. Underneath the basement membrane is the intima, which separates ECs from the internal elastic laminae (IEL) formed by several layers of contractile vascular smooth muscle cells (SMCs) and separated by elastic fibers and collagen-rich ECM. Under the basement membrane, normal vessels contain minimal intima, and instead contain media beginning at the IEL, followed by concentric lamellar units composed of elastic fibers and SMCs separated by interlaminar matrix collagens, microfibrils, proteoglycans, glycoproteins, and ground substance [4] — although the media components can be different between different types of blood vessels. Arteries, for example, have more collagens and elastin than veins have. Outside the SMC layer of large vessels is an adventitial layer extending beyond the external elastic laminae and interstitial matrix that contains fibrillar types I and III collagen, chondroitin sulfate and dermatan sulfate proteoglycans, fibronectin, and many other ECM proteins.

The same ECM proteins at different regions of the blood vessel wall may come from different cells and be regulated by different modulators under certain circumstances. Collagen and elastin in the media are produced primarily by SMCs. TGF-β1 stimulates SMC proliferation, migration, and ECM expression, leading to luminal narrowing [5]. Attenuating TGF-β1 activity with tranilast, TGF-β3, or directly with TGF-β1 inhibitors diminishes intima SMC proliferation-associated thickening, often called blood vessel stenosis or restenosis [6,7]. In the adventitia,

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however, ECMs — such as collagen, osteopontin, and fibronectin — primarily come from fibroblasts, as in other connective tissues. In cultured rat adventitial fibroblasts, vascular endothelial growth factor (VEGF) regulates the expression of osteopontin, an integrin recognition sequence arginine–glycine–asparagine (RGD)-containing ECM phosphoprotein that mediates leukocyte cell adhesion and migration, and prevents cell apoptosis.

Different ECM proteins form different types of blood vessels. Mature vessel wall ECM is a complex arrangement of fibrous proteins, associated with glycoproteins embedded in a hydrated ground substance of glycosaminoglycans and proteoglycans. Normal large arteries also contain collagen, elastin, fibronectin, and small amounts of osteopontin, thrombospondin, and tenascin. Vessel wall remodeling occurs as an adaptation to pressure and flow (e.g., vein graft) or to mechanical (e.g., angioplasty) or biochemical (e.g., atherosclerosis) injuries, all of which promote ECM-regulated SMC migration and proliferation [8]. Arterial SMCs also synthesize vitronectin. Normal quiescent vessels contain only low levels of interstitial vitronectin and fibronectin. Vitronectin receptor $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins, and fibronectin receptor $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins, are suppressed in quiescent SMCs [9]. In normal arteries, apolipoprotein E (ApoE) and ApoE-containing high-density lipoprotein (HDL) maintain arterial elasticity by controlling the expression of ECM, reducing the expression of collagen-1, fibronectin, and the elastin/collagen cross-linking enzyme lysyl oxidase in response to substratum stiffening. In angiogenic vessels, however, fibronectin also becomes a predominant constituent of the endothelial basement membrane. Angiogenic vessels, but not quiescent vessels, also contain fibronectin alternative spliced variants: extra domain-A (ED-A) and extra domain-B (ED-B).

1.2. ECM functions

ECM is not an inert supporting network, but rather an active and dynamic structure with a fundamental role in regulating vascular function in normal and pathological conditions. One ECM protein may regulate the production of others. Homeostasis of the vascular ECM may affect intrinsic properties of the arterial wall and arterial stiffness. When elastin scaffold and collagen scaffold were prepared from porcine ascending aortas [10], and implanted subdermally into live rats for 28 days, porcine elastin scaffolds contained enhanced rat collagen fibers and bundles, and porcine collagen scaffolds contained elevated rat elastin fibers — indicating that elastin and collagen support de novo ECM synthesis [11].

Cellular interaction with ECM regulates cell adhesion, migration, proliferation, phenotype, and tissue architecture under different circumstances. From in vitro prepared SMCs, total insoluble ECM proteins stimulate RAW264.7 or thioglycolate-elicited macrophage extracellular signal regulated kinase-1/2 (EKR1/2) activation, cyclooxygenase (COX)-2 and prostaglandin (PG) E2 syntheses, and protease (e.g., urokinase plasminogen activator [uPA] and matrix metalloproteinase [MMP]-9) expression. The selective COX-2 inhibitor NS398 blocked ECM-induced protease expression. Macrophages from COX2-deficient mice showed reduced responses to SMC-ECM, demonstrating that COX-2 is an ECM target [12]. Vascular cells use matrix receptors such as integrins to detect changes in matrix rigidity and composition that occur during tissue remodeling. The resulting intracellular signaling then regulates cellular processes such as proliferation, survival, differentiation, and gene expression [13]. The basal laminae proteins collagen-IV, laminin, and perlecan limit SMC growth, enhance contractile gene expression, reduce inflammatory gene expression, reduce low-density lipoprotein (LDL) uptake in culture, and inhibit matrix calcification. In contrast, interstitial matrix proteins — such as collagen-I, collagen-III, fibronectin, and osteopontin — enhance SMC growth concomitant with elevated ERK phosphorylation and expression of cell cycle regulators [14,15]. Inhibiting the integrins that bind to these interstitial matrix proteins sufficiently blocks SMC proliferation in response to platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF) [16], and reduces migration and neointima formation in vivo [17]. Collagen-IV, polymerized collagen-I, proteoglycans, and media elastin limit SMC growth and promote a contractile phenotype, whereas monomeric collagen-I reduces contractile gene expression.

As we will discuss further later, damage to ECM components contributes to the development of vascular diseases. ECM components such as elastin and proteoglycans undergo fragmentation or physiochemical alteration during atherogenesis. Chemically modified ECM or enzymatically degraded ECM may change the activities of parental ECM, thereby promoting ECM remodeling and vascular disease pathogenesis. Many ECM subdomains have roles independent of the parental ECM molecules; they therefore are often called matrikines, and have pathophysiological functions. Fragments from the noncollagenous (NC1) domain of the type IV collagen $\alpha 1$, $\alpha 2$, and $\alpha 3$ chains (also known as arresten, canstatin, tumstatin), type XV collagen (also known as restin), and type VXIII collagen (also called endostatin) all have anti-angiogenic activities to block neovascularization [18,19]. Production of these matrikines directly affects the angiogenesis that plays physiological roles in embryogenesis and pathological roles in tumor growth, atherogenesis, abdominal aortic aneurysms (AAAs), varicose veins, hypertension, and many other large and small artery and vein disorders.

2. Elastin

Mature elastin is an insoluble and hydrophobic protein formed by cross-linking of its precursor, tropoelastin — a 68–74 kDa monomeric protein from elastin mRNA alternative splicing normally produced by SMCs in the media and by fibroblasts in the adventitia, released to the extracellular space for cross-linking and elastin fiber formation with the assistance of lysyl oxidase and the helper proteins fibulin-4 or -5. Elastin deposition is limited to the media layer extending from the internal to external elastin laminae. Elastin is the dominant ECM in the arterial wall, comprising 50% of its dry weight [20], and is the largest component of elastic fiber, comprising ~90% of elastic fiber total weight. Elastin fiber consists of fibrillin microfibrils and is embedded within an amorphous core of elastin that allows the elastic recoil. Arteries are subject to extensive mechanical stress induced by arterial blood pressure. In addition to mechanical integrity, elastic laminae contribute to the elasticity of the arteries. Recoil of the arterial wall therefore is a critical mechanism for the continuation of blood flow during diastole when cardiac ejection is ceased. Fibrillin-rich microfibrils provide a structural scaffold to guide elastin deposition and assembly. Elastic fibers are found throughout the vessel wall in the medial layer, where they arrange in concentric fenestrated elastic laminae. Each elastic lamina alternates, and is physiologically connected with a concentric ring of SMCs, forming the lamellar unit — the functional resilient unit of the arterial wall [21,22].

Under normal conditions, elastogenesis is restricted mainly to fetal life and infancy, and mature elastic fibers last for the entire lifespan. The half-life of elastin fibers is about 40 years; elastic fibers are considered the most durable element of ECM [23]. Elastic fibers are degraded and fragmented with age and disease, leading to increased stiffness of the arterial wall [24]. Under pathological conditions, vascular cells (SMCs, ECs, and fibroblasts) make elastin as part of the reaction to increased mechanical stress [25]. In addition to vascular cells, inflammatory cells also produce tropoelastin, but these tropoelastins fail to cross-link into elastic fibers [26].

2.1. Elastin expression, cross-linking, and assembly

The human tropoelastin gene is located on chromosome 7. Its expression can be regulated differently in response to different cytokines, growth factors, or other bioactive molecules. Insulin-like growth factor (ILGF), transforming growth factor (TGF)-$\beta 1$, cGMP, and nitric oxide