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Review Article

Elastin microfibril interface–located protein 1, transforming growth factor beta, and implications on cardiovascular complications

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Abstract

Elastin microfibril interface–located protein 1 (EMILIN1), a glycoprotein, is associated with elastin in the extracellular matrix (ECM) of arteries, lymph vasculature, and other tissues. EMILIN1 particularly has a niche role in elastin fiber biogenesis (elastogenesis) by aiding with the fusion of elastin fibers, rendering them more ordered. In addition to elastogenesis, EMILIN1 has been shown to have roles in maintenance of vascular cell morphology, smooth muscle cell adhesion to elastic fibers, and transforming growth factor (TGFβ) regulation, by inhibiting TGFβ activation via blocking the proteolytic production of the latency-associated peptide/active TGFβ complex. The increased TGFβ signaling induced during EMILIN1 deficiency alters TGFβ activity, resulting in vascular smooth muscle cell growth and vascular remodeling. The increasing systemic blood pressure associated with TGFβ signaling may be closely linked to the activity of other mediators that affect cardiovascular homeostasis, such as angiotensin II. The increase in prevalence of hypertension and other cardiovascular diseases in other disease states likely involve a complex activation of TGFβ signaling and ECM dysfunction. Thus, the interaction of TGFβ and ECM components appears to be integrative involving both structural alterations to vessels through EMILIN1 and changes in TGFβ signaling processes. This review summarizes the current knowledge on the EMILIN1–TGFβ relationship; the specific roles of EMILIN1 and TGFβ in blood pressure regulation, their synergistic interaction, and in particular the role of TGFβ (in conjunction with ECM proteins) in other disease states altering cardiovascular homeostasis. J Am Soc Hypertens 2017;■(■):1–12.

Keywords: Disease interaction; genetic predisposition; hypertension; vascular integrity.

Introduction

The vascular extracellular matrix (VECM), produced by smooth muscle cells (SMCs) of the vessel wall, is made up of a highly organized composition of three primary structural and functional proteins[1]—elastin, collagen, and various proteoglycans, with vascular fibroblasts lending structural support and matrix remodeling within the VECM.[2] As a unit, the VECM creates the structural framework within the vessel wall, is able to actively facilitate cellular responses, and maintains homeostasis in the various organs of the body.[3–5] The complex composition and molecular interactions of protein components within the VECM in maintaining physiological function is not fully understood. To date, research has focused on the more common biomolecules mentioned previously, with less attention given to certain *modifiers* of the VECM, such as the elastin microfibril interface–located protein (EMILIN) family matrix proteins. We are starting to understand how the structure and function of EMILIN

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(particularly EMILIN1) contribute to general vascular homeostasis and the consequence of alterations to EMILIN1 in particular to cardiovascular homeostasis.

The original function attributed to EMILIN was in preserving skin integrity. Within the cardiovascular system, the protein affects arterial blood pressure (BP), decreases vessel lumen diameter, promotes angiogenesis, and maintains platelet homeostasis.[6] Overall, however, the primary mechanism attributed to vascular regulation involves EMILIN1's direct relationship with transforming growth factor β (TGFβ), to significantly affect vascular myogenic function in response to increases in mechanical stress.[7] The direct involvement of EMILIN1, particularly its capacity to maintain vessel wall integrity and elasticity in cardiovascular homeostasis, especially in chronic disease conditions, has not been considered. Extensive and permanent changes occur as a result of disease progression into a chronic state, and interactions with other mediators compound the damage incurred. EMILIN1, in combination with TGFβ, may have a role in the pathogenesis of chronic diseases and essential hypertension and be involved in directly potentiating other cardiovascular pathologies, such as loss of blood flow autoregulation in the brain vasculature, leading to development of stroke.[8] We aim to first define what is known about structure and function of both EMILIN1 and TGFβ in relation to the cardiovascular system and further clarify the various roles they play in vascular homeostasis, particularly its modified role in disease states.

EMILIN Protein Structure and Expression Patterns

There are currently five known isoforms in the EMILIN family of glycoproteins which are primarily localized to the extracellular matrix (ECM). Structurally, EMILIN1, EMILIN2, EMILIN3, Multimerin1, and Multimerin2 share an N-terminal cysteine-rich EMI domain, composed of approximately 80 amino acids, followed by a coiled-coil domain (approximately 700 amino acids). The structural similarities suggest functional overlaps, with the unique additional domains designating specialized functions or allowing distinct distribution patterns throughout different developmental stages.[9–12] All EMILINs, excluding EMILIN3, also have a globular C1q (gC1q) domain located at the C-terminal end.[6,13] gC1q plays a major role and is the main adhesive substrate of the EMILIN1 protein, allowing the protein to interact with the $\alpha4\beta1$ and $\alpha9\beta1$ integrin. This interaction is of significance in cell adhesion, migration, proliferation, and all processes involved in maintaining skin and vessel integrity, elasticity, and cellular differentiation of various tissues in the body.[6,14] The interaction of gC1q domain of EMILIN with the $\alpha9\beta1$ integrin is also seen in the lymphatic system and the hyperplasia and enlargement of lymphatic vessels in EMILIN1$^{-/-}$ mice; the altered lymphatic vascular morphology indicates EMILIN1 has a direct role in the growth, maintenance, and integrity of the lymphatic vasculature as well.[3] Studies showing degradation of EMILIN1 by neutrophil elastase in the lymphedema model also indicate that EMILIN1 provides baseline level of vessel integrity and stability with anchoring filaments in other vessels.[15]

The functional relevance of all the EMILIN subtypes in the cardiovascular system has yet to be fully elucidated, but the expression is generally limited to the ECM. EMILIN1 gene is expressed in the endocardium, the right ventricle myocytes and the one most indiscriminately expressed in the vascular system, by cells of the entire blood vessel wall (endothelial cells [ECs], SMCs, and adventitial fibroblasts).[12] EMILIN1$^{-/-}$ mice studies suggest there is a specific role in maintaining vascular homeostasis.[16–18] EMILIN2 expression is identified within cells and ECM by immunohistochemistry in the carotid and aorta. EMILIN2 appears to be linked more specifically to cardiac tissue, and is higher during cardiovascular development, particularly in cardiac stem cells and heart tissue of heart disease models.[19] Interestingly, EMILIN3 was not found to be expressed at all in the cardiovascular system.[13] The variability in EMILIN1 and EMILIN2 expression patterns within the cardiovascular system likely leads to functional differences, with direct interaction between EMILIN subtypes implicated in maintaining cardiovascular homeostasis. Information on EMILIN2 expression and its role in cardiovascular function is sparse, although there has been a recent resurgence of interest in the protein because of its role in thrombosis. Patients who have partial, or complete deletions in chromosome 18 (in human), where EMILIN2 is located, exhibit cardiac malformations. Experiments with EMILIN2$^{-/-}$ mice and studies in deletions of chromosome 17 in mice also indicate EMILIN2's role in inducing platelet aggregation, particularly those induced by adenosine diphosphate, collagen, and thrombin.[19–21] What is remarkable is that EMILIN1 appears to attenuate the effects of EMILIN2 on platelet aggregation and thrombosis, suggesting opposite roles of the two EMILIN subtypes in pathogenesis of platelet aggregation. It also suggests a direct interaction between the two proteins likely occurs to maintain cardiovascular homeostasis. Indeed, recent investigation of EMILIN1 and EMILIN2 assembly and interaction, using two hybrid systems corresponding to the gC1q and EMI domains, indicate that the gC1q domains expressed in EMILIN likely play a significant role in the interaction, assembly, and differential expression of EMILIN in various tissues. EMILIN1 appears to attenuate the direct effects of EMILIN2 on platelet aggregation and thrombosis, suggesting opposite roles of the two EMILIN subtypes in pathogenesis of platelet aggregation.[19,22]