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Vasculogenesis and Angiogenesis: Extracellular Matrix Remodeling in Coronary Collateral Arteries and the Ischemic Heart

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Abstract Heart failure secondary to ischemic cardiomyopathy is the primary cause of cardiovascular mortality. The promise of the collateral circulation lies in its potential to alter the course of the natural history of coronary heart disease. The collateral circulation of the heart is responsible for supplying blood and oxygen to the myocardium at ischemic risk following severe stenosis and reduced vasoelasticity function of a major coronary artery. In response to flow, stress, and pressure, collateral vessels are restructured and remodeled. Vascular remodeling by its very nature implies synthesis and degradation of extracellular matrix components in the vessel wall. Under normal physiological conditions proteinases that break down the specialized matrix are tightly regulated by antiproteinases. The balance between proteinase and antiproteinase influences is discoordinated during collateral development which leads to adaptive changes in the structure, function, and regulation of extracellular matrix components in the vessel wall. The role of extracellular matrix components in coronary collateral vessel formation in a canine model of chronic coronary artery occlusion has been demonstrated. The role of matrix proteinases and antiproteinases in the collateral vessel play a significant role in the underlying mechanisms of collateral development. This review presents new and significant information regarding the role of extracellular matrix proteinases and antiproteinases in vascular remodeling, function, and collateral development. Such information will have a significant impact on the understanding of the basic biology of the vascular extracellular matrix turnover, remodeling, and function as well as on elucidating potential avenues for pharmacological approaches designed to increase collateral formation and optimize myocardial blood flow in the treatment of ischemic heart disease. J. Cell. Biochem. 65:388–394.

Key words: angiogenesis; vasculogenesis; collateral; vessel; development; occlusion; extracellular matrix; collagenase; collagen; heart failure; matrix metalloproteinase; tissue inhibitor of metalloproteinase; growth factors

Development of coronary collateral circulation is the heart's own bypass mechanism by which it retains the blood supply to the myocardium at risk. Angiogenesis is a structural and morphogenetic process by which new vessels are generated by sprouting from existing blood vessels [1]. Collateral arteries develop rapidly following chronic occlusion of a major coronary artery [2], and collaterals play a critical role in reestablishing and maintaining blood flow to the ischemic myocardium (collateral-dependent myocardium) [3,4]. These collateral vessels are responsible for maintaining the nutrient supply to the ischemic heart. The specific mechanisms by which collaterals are formed in the adult heart are largely unknown. Mechanisms that regulate metabolism of extracellular matrix (ECM) play a very important role during angiogenesis [16,29]. We have shown that dynamic changes in the ECM components and concentrations take place in the collateral formation [12]. Coexpression of extracellular matrix metalloproteinases (MMP) and tissue inhibitor of metalloproteinase (TIMP) at the mRNA and protein levels in the normal myocardium has been suggested [5,6]. However, in

Abbreviations used: bFGF, basic fibroblast growth factor; ECM, extracellular matrix; LAD, left anterior descending artery; LCx, left circumflex; MMPs, matrix metalloproteinases; PAI, plasminogen activator inhibitor; PMSF, phenyl methyl sulfonyl fluoride; TGFβ, transforming growth factor; phen, phenanthroline; TIMPs, tissue inhibitor of metalloproteinases; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.

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ischemic heart the TIMP-1 and -2 levels were reduced and the MMP levels were increased in the infarcted area [7]. Collaterals are formed at and near the infarct border zone. Collateral formation was induced in the ischemic heart and infarct size was reduced by angiogenic factors such as heparin [8,9]. In coronary arteries, Tyagi et al. [10] have demonstrated that collagen is induced and elastin is repressed during atherosclerotic and restenotic processes. Collectively these studies indicated that a critical balance existed among matrix, proteinase, and antiproteinase locally and that the ECM dynamics regulates vascular function [32,50]. Remodeling in the collateral vessel wall is in part responsible for the adaptive nature of these important vessels. The MMP and inhibitor TIMPs may play a very critical role(s) in the tissue remodeling process of collaterals and collateral-dependent myocardium. The role of MMP in restructuring of the ECM following collateralization has not been explored. In order to develop the means of increasing collateral circulation, it is of great importance to identify the cascade of remodeling and catalogue the ECM factors involved in coronary collateral vessel remodeling. We have demonstrated that MMP and their ECM-degradation products are in part responsible for productive remodeling and angiogenic activity in the coronary collateral arteries [11,12].

Altered vasomotor function of coronary collateral arteries has been observed during the insult to the myocardium due to chronic coronary occlusion. Rapps et al. [13,14], Peters et al. [15], and Angus et al. [16] have all demonstrated that collateral arteries exhibit altered vasoconstriction responsiveness to endothelin and vasopressin and that collateral arteries exhibit altered mechanisms of endothelium-dependent vasodilatation. The molecular mechanism(s) of altered collateral function is not well understood. It is possible that the ECM peptide generated in situ following remodeling in the collateral arteries is responsible in part for altered vascular function in coronary collateral vessels. In this regard the understanding of ECM peptide in regulation of vascular tone is of great importance. The understanding of extracellular matrix regulation of vascular structure and function and identification of new vasorelaxing factors derived from extracellular matrix is required for the understanding of structure controlling function.

Endothelial cells are critically involved in control of vascular tone [17]. These cells are invasive and migrate through the matrix barrier during angiogenesis and the development of new blood vessels [18]. However, their role in ECM remodeling is not fully understood. These endothelial cells require the elaboration of synthesis of new matrix components and matrix-degrading proteolytic enzymes, which include neutral MMP such as collagenases, and serine proteinases such as plasminogen activators (PA) [19]. Endocardial endothelial cells produce ECM components in response to serum-containing growth factors [20]. It is important to determine if the phenotypic differences in the endothelial cells isolated from collateral and noncollateral coronary arteries and their different angiogenic responsiveness to ECM peptide are due to adaptive/maladaptive changes following vasculogenesis. These studies have potential to identify an ECM component which could be used as an angiogenic factor for the increase of collateral formation following myocardial ischemia and heart failure.

ROLE OF EXTRACELLULAR MATRIX TURNOVER/REMODELING IN COLLATERAL DEVELOPMENT

Occlusion of a major coronary artery initiates the development of a collateral circulation [21]. Collateral arteries are derived from native, thin-walled, narrow-channeled coronaries (vasculogenesis). Following occlusion, these important vessels rapidly increase their luminal size and undergo significant long-term structural remodeling and develop the morphological appearance of small arterioles but differ in several characteristics, including extracellular matrix restructuring [11,12,16]. Proteoglycans, including heparin sulfates, constitute a part of the ECM that participates in cell adhesion, migration, and proliferation [51]. Fibronectin which embeds fibrillar collagens and vascular cells is increased 24 h after collateralization [22]. Collagen labelling showed a slight increase level at week 1, but after week 4 the level increased profoundly [22]. We for the first time demonstrated increased levels of MMP and decreased levels of TIMP-1 and -2 in collateral formation [11,12]. The level of urokinase-plasminogen activator [uPA] was found to be increased in the swine myocardium during coronary artery occlusion [23]. This study, however, did not measure the level of uPA in the isolated coronary collat-

eral arteries. In our canine model of chronic coronary occlusion, we measured PA specifically in isolated epicardial collateral arteries devoid of interstitial tissue [11,12]. Remodeling implies tight regulation of specialized proteinases and antiproteinases which modulate ECM turnover (synthesis and degradation). It will be necessary to identify the mechanism and the factor(s) responsible for collateralization in order to develop the means of prevention of ischemic insult to the myocardium at risk. We have shown that a balance between ECM synthesis and degradation exists in the normal coronary arteries [10]. We have demonstrated that the balance equilibrium among ECM/proteinase/antiproteinase which normally exists is disturbed during ECM remodeling in the coronary collateral artery when compared with noncollateral vessels [12].

EXTRACELLULAR MATRIX REGULATION OF COLLATERAL AND NONCOLLATERAL VASCULAR FUNCTION

Structurally, we observed more thickening of intima in the collateral vessels than normal vessels [11,12,16]. Vascular wall thickness increased over the 4 month period. There was no significant change in the media of collateral and LAD. However, the ratio of intima/media increased over time [12]. These results suggest that the thickening of arterial wall may be the compensatory response, to pressure load, of the tissue in widening the vessel during the development of collaterals. In addition, these vessels differ from noncollateral arteries in pharmacological reactivity to various vasodilator and constrictors [24]. For instance, collateral vessels appeared to be more reactive to vasopressin than the normal arteries both in vivo and in vitro [24]. Also, small vessels (100–200 μm) serving collateral-dependent myocardium contracted more strongly to vasopressin as compared to control vessels [25]. Collateral-dependent vessels had markedly impaired relaxation responses to acetylcholine but enhanced relaxation responses to nitroglycerin [25]. The functional [24,25,50] and the structural [12,16] studies may suggest that the components, such as elastin peptide, already present in the collateral vessels are responsible for this unique feature of these important vessels. Elastin peptide inhibits Ca^{2+} loading into the vascular cells; therefore, the elastin peptide inhibits the atherosclerotic process [26]. Also, elastin peptide regulates Ca^{2+} mobilization in neutrophils [27], suggesting a functional role of elastin peptide in vessels wall. Elastin breakdown products have been observed in coronary collaterals and are unique to these vessels, not found in the noncollateral vessels [11,12,16]. The role of the elastin peptide in the functional properties of the collateral and noncollateral vessels is not known. It is possible that the elastin peptide generated during remodeling induces vasorelaxing activity in collateral vessels and that therefore the collateral vessels are less responsive to acetylcholine and other vasodilators. We suggest that the structural changes in extracellular matrix following remodeling lead to alterations in the vascular tone of these important vessels. Also, heparin, an ECM component, induces cellular proliferation by increasing calcium infux [28] and plays an important role in modulation of coronary collateral reactivity [9]. The effect of ECM degradation in collateral and noncollateral artery function (vasoconstriction/relaxation) may have significant implications for the therapeutic advancement of the treatment of chronic ischemic heart disease and heart failure (Fig. 1A).

ANGIOGENIC FACTORS AND THEIR ROLE IN CELLULAR METABOLIC FUNCTION DURING COLLATERAL DEVELOPMENT

Under conditions of physiological angiogenesis, vascular endothelial cells experience a different extracellular matrix environment depending on whether the cells are in a resting state or are undergoing sprouting and migration. In the normal, quiescent state, endothelial cells rest on a specialized extracellular matrix, the basement membrane, which contains predominantly elastin, type IV collagen, and laminin. During angiogenesis, the cells focally degrade their investing basement membrane and subsequently migrate into the interstitial matrix of the surrounding connective tissue which consists mainly of type I collagen [29]. Matrix-degrading proteolytic enzymes which include neutral metalloproteinases, such as collagenase, and serine proteinases, such as tPA, are involved in endothelial cell migration [30]. We observed elongated endothelial cells in collateral vessel as compared to noncollateral arteries [11,12], suggesting a role of ECM dynamics in the changes of cell phenotype.

ECM is composed of proteinase/antiproteinase, elastin, collagen, and proteoglycans and

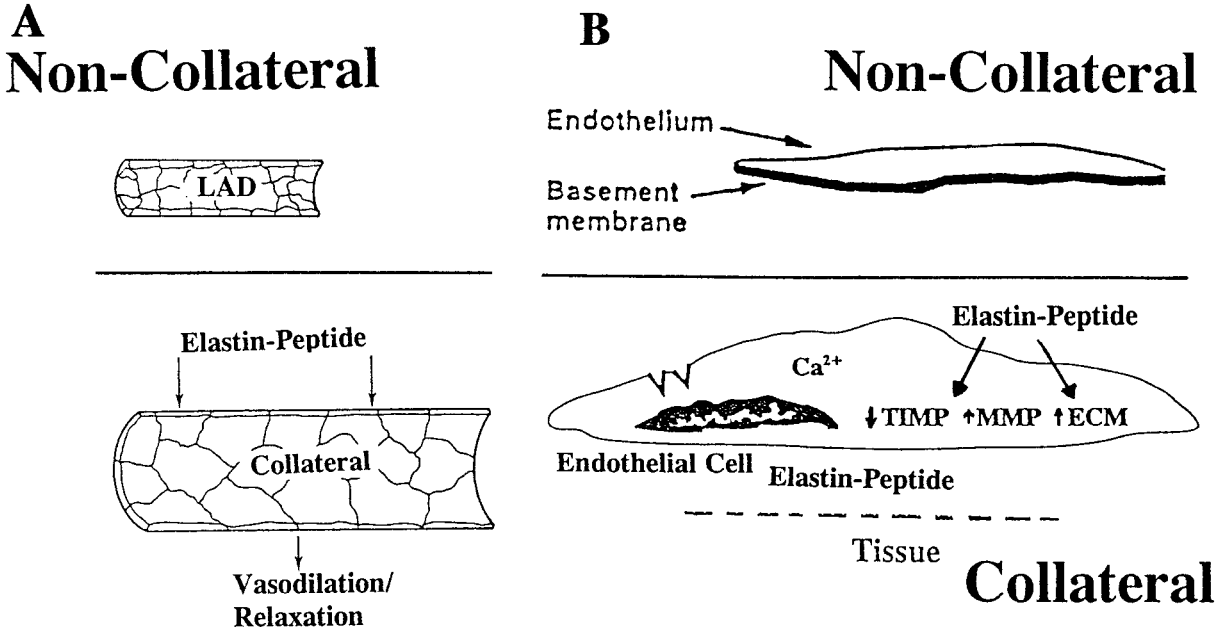

Fig. 1. **A:** Role of ECM-degradation products in vascular function. Elastin peptide induces vasodilatation and vasorelaxation. This figure suggests that induction of a vessel with elastin peptide induced vasorelaxation. **B:** Endothelial cells are more elongated in collateral vessels than noncollateral vessels. A role for ECM-degradation peptides in the induction of matrix components in collateral and noncollateral endothelial cells is shown.

growth factors. During remodeling, proteinases break down ECM and release growth factors. Elastase-released growth factors from ECM are implicated in collateral formation [31]. Naturally, since elastin is a component of the ECM, elastase and MMPs also release the elastin peptide from ECM [32,33]. Vascular endothelium controls arterial tone [17] and synthesizes MMPs and metalloelastase [34,35]. The role of growth factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) in collateral formation has been elaborated extensively [36,37]. It has been suggested that FGF and VEGF are angiogenic, whereas TGFβ is antiangiogenic to many cells [38]. The TIMP-1 and -2 are mitogenic to endothelial cells it inhibits cellular proliferation as well [39]. The ECM synthesis and degradation is the essential first step in the remodeling process which generates the elastin peptide. Elastin peptide plays a significant role in cellular proliferation [40,44]. The role of elastin peptide has been demonstrated in vascular function [50]. It is not known whether elastin peptide is an angiogenic factor. It is of great interest to show that the elastin peptide contains angiogenic activity to collateral endothelial cells.

Elastin peptides exert chemoattractive effects on human monocytes and fibroblasts [41]. Proteinases exhibiting elastinolytic activity have been implicated in the disappearance of elastic fibers which occurs with aging [42]. The smooth muscle expression of elastinolytic enzymes (gelatinase A and B) was found to be increased by elastin peptide [34,43]. It is known that the elastin peptide is a stimulator of ECM synthesis [42]. Previously, we have demonstrated that the elastin peptide induces MMP expression in fibroblast cells [44]. In collateral vessels, elastin peptide is elevated [11,12,16], and it is possible that elastin peptide stimulates endothelial cell proliferation, migration, and matrix invasion and matrix induction of MMP expression. It is possible that the elastin peptide induces vascular endothelial MMP expression and also an adaptive response leading to remodeling in the coronary collateral arteries (Fig. 1B).

In the infarcted heart, heparin induces angiogenesis near the infarct border zone [45], and

collaterals are formed in the noninfarcted heart. We have shown that heparin induces MMP expression in fibroblast cells [28]. The fibroblasts transform into myofibroblast cells during remodeling and angiogenesis [46]. In contrast to this, heparin inhibits smooth muscle proliferation by inhibiting MMP expression [47]. This suggested a differential specific role of heparin in different cells (i.e., increase MMP expression during angiogenesis and repress MMP levels during intimal growth following vascular injury). Collectively, these reports suggest that the ECM components play a specific role in specific tissue and environment.

CONCLUSIONS

Coronary heart disease is the primary cause of cardiovascular death. Occlusion of a main coronary depletes the blood supply to the myocardium and subsequently reduces cardiac function which ultimately leads to heart failure. Progressive, chronic coronary artery occlusion has been shown to induce development of collateral arteries to reestablish and maintain blood flow to the myocardium at risk via the growth of new capillary vessels (angiogenesis) and the enlargement of preexisting vessels. Studies in experimental animals and in humans have confirmed the protective role of collaterals against myocardial ischemia, myocardial infarction, and cell death [48]. Even after myocardial infarction, collateral blood flow significantly improves recovery of the function of the infarct zone [49]. Indeed, the collateral circulation is the most effective natural defense mechanism of the diseased heart. There is no concept under evaluation today that has as its declared aim the understanding of the molecular mechanisms and extracellular matrix remodeling process which initiate the cascade of events that lead to formation of the coronary collateral arteries. The powerful therapies of ischemic heart disease like coronary bypass surgery and angioplasty are being used; these treatments are invasive and expensive and not without risk. A noninvasive therapy directed at improvement of the collateral circulation could provide a solution to ischemic heart disease and heart failure. In view of the important protective role of the collateral circulation, delineation of the cellular mechanisms which mediate vascular structural remodeling, contractile and dilatory function, and thus maintain blood supply represents a significant aspect of this review. The understanding of structural components induced in collateral development will lead to identification of the factor(s) required for the development of these important vessels. The factors identified, in the future, will be used as the means of increasing collateral circulation in the myocardium at risk and to restore the blood nutrients to the diseased heart secondary to ischemic insult and/or coronary heart disease and heart failure.

We have demonstrated that most of the MMP in the normal vessels are in the latent form and are decreased during atherosclerotic and restenotic processes and increased during collateral formation [10,11,12]. It is of great importance to identify the factors that induce phenotypic adaptive changes in the vascular endothelial cells which lead to changes in ECM quantity and composition as well as vascular remodeling, furthermore leading to the development of collateral arteries. The identified intrinsic vascular ECM-derived angiogenic factors (for example, elastin peptide and new growth factors) will be used as potent therapeutic agents for the treatment of the animal model of ischemia and heart failure and eventually human coronary heart disease. It is of great interest to demonstrate the direct role of elastin peptide on the heart. The application of the therapies to increase elastin turnover in the ischemic heart which will also ultimately increase elastin peptide will be useful to increase collateral circulation in the myocardium at ischemic risk and heart failure.

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REFERENCES

1. Folkman J, Klagsbrun M (1987): Angiogenic factors. Science 235:442–448.
2. Pasyk S, Flameng W, Wusten B, Schaper W (1976): Influence of tachycardia on regional myocardial flow in chronic experimental coronary occlusion. Basic Res Cardiol 71:243–251.
3. Risau W, Ekblom P (1986): Growth factors and the embryonic kidney. In Serino D (ed): "Progress in Clinical and Biological Research, Hormonal Control of Embryonic and Cellular Differentiation." New York: Liss, pp. 221–232.
4. Schaper W (1991): Angiogenesis in the adult heart. Basic Res Cardiol 86:51–56.

5. Tyagi SC, Matsubara L, Weber KT (1993): Direct extraction and estimation of collagenase(s) activity by zymography in microquantities of rat myocardium and uterus. Clin Biochem 26:191–198.
6. Tyagi SC, Kumar SG, Banks J, Fortson W (1995): Co-expression of tissue inhibitor and matrix metalloproteinase in myocardium. J Mol Cell Cardiol 27:2177–2189.
7. Tyagi SC, Reddy HK, Campbell SE, Weber KT (1995): Myocardial collagenase in failing human heart. In Weber KT (ed): "Wound Healing in Cardiovascular Disease." Boston: Futura Publishing Co., pp 67–72.
8. Uchida Y, Yanagisawa-Miwa A, Ikuta M, Makamura F, Tomaru T, Fujimori Y, Morita T (1994): Angiogenic therapy of acute myocardial infarction (AMI) by intrapericardial injection of basic fibroblast growth factor (bFGF) and heparin sulfate (HS): An experimental study. Circulation 90:4, part 2, I-296.
9. Carroll SM, White FC, Roth DM, Bloor CM (1993): Heparin accelarates coronary collateral development in a porcine model of coronary artery occlusion. Circulation 88:198–207.
10. Tyagi SC, Meyer L, Schmaltz RA, Reddy HK, Voelker DJ (1995): Proteinases and restenosis in human coronary artery: Extracellular matrix production exceeds the expression of proteolytic activity. Atherosclerosis 116:43–57.
11. Tyagi SC, Borders S, Kumar SG, Cassatt S, Parker JL (1995): Expression of matrix metalloproteinase activity in coronary collateral arteries. Circulation 92(Suppl):I-169.
12. Tyagi SC, Kumar SG, Cassatt S, Parker JL (1996): Temporal expression of extracellular matrix metalloproteinase and tissue plasminogen activator in the development of collateral vessels in canine model of coronary occlusion. Can J Physiol Pharmacol 74:983–995.
13. Rapps JA, Magliola L, Jones AW, Parker JL (1993): Impaired endothelin-induced contraction in coronary collateral arteries. Circulation 88:I-36.
14. Rapps JA, Zhong Q, Myers PR, Parker JL (1994): Development of endothelium-dependent relaxation in canine coronary collateral arteries. Circulation 90:I-459.
15. Peters KG, Marcus ML, Harrison DG (1989): Vasopressin and the mature coronary collateral circulation. Circulation 79:1324–1331.
16. Angus JA, Ward JE, Smolich JJ, McPherson GA (1991): Reactivity of canine isolated epicardial collateral coronary arteries (Relation to vessel structure). Circ Res 69:1340–1352.
17. Furchgott RF (1990): Endothelium-derived relaxing factor: Some old and some new findings. In Moncada S, Higgs EA: (eds): "Nitric Oxide From L-Arginine: A Bioregulatory System." Amsterdam: Elsevier Science Publishing Co., Inc., pp 5–17.
18. Folkman J, Haudenschild C (1980): Angiogenesis in vitro. Nature 288:551–553.
19. Ausprunk DH, Folkman J (1977): Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during angiogenesis. Microvasc Res 14:53–65.
20. Tyagi SC, Kumar SG, Glover G (1995): Induction of tissue inhibitor and matrix metalloproteinase by serum in human heart-derived fibroblast and endomyocardial endothelial cells. J Cell Biochem 58:360–371.
21. Schwartz F, Wayner HD, Sesto M (1982): Native collaterals in the development of collateral circulation after chronic coronary stenosis in mongrel dogs. Circulation 66:303–308.
22. Schaper J, Weibrauch D (1993): Collateral vessel development in the porcine and canine hearts. In Schaper W, Schaper Z (eds): "Collateral Circulation." Boston, Dordrecht, London: Kluwer Academic Publishers, pp 65–102.
23. Knoepfler PS, Bloor CM, Carroll SM (1995): Urokinase plasminogen activator activity is increased in the myocardium during coronary artery occlusion. J Mol Cell Cardiol 27:1317–1324.
24. Harrison DG, Chilian WM, Marcus ML (1986): Absence of functioning α-aderengic receptor in mature canine coronary collaterals. Circ Res 59:133–142.
25. Sellke FW, Wuilen JE, Brooks LA, Harrison DG (1990): Endothelial modulation of the coronary vasculature in vessels perfused via mature collaterals. Circulation 81:1938–1947.
26. Yosiyuki K, Okuda H (1988): Inhibitory effects of soluble elastin on intraplatelet free calcium concentration. Thromb Res 52:61–64.
27. Varga Z, Kovacs EM, Paragh G, Jacob M-P, Robert L, Fulop T (1988): Effect of elastin peptides and N-formylmethionyl-leucyl phenylalanine on cytosolic free calcium in polymorphonuclear leukocytes of healthy middle-aged and elderly subjects. Clin Biochem 21:127–130.
28. Tyagi SC, Kumar S, Kawta L (1997): Differential regulation of matrix metalloproteinases and tissue inhibitors by heparin and cholesterol in human heart fibroblast cells. J Mol Cell Cardiol 29:391–404.
29. Iruela-Arispe ML, Diglio CA, Sage EH (1991): Modulation of extracellular matrix proteins by endothelial cells undergoing angiogenesis in vitro. Arterioscl Thromb 11:805–815.
30. Moscatalli D, Rifkin DB (1988): Membrane and matrix localization of proteases: A common theme in tumor invasion and angiogenesis. Biochim Biophys Acta 948: 67–85.
31. Halperin F, Thompson K, Rabinovitch M (1995): Elastase-mediated release of extracellular matrix-bound basic fibroblast growth factor: Implications in coronary collateral development. Circulation 92:I-168.
32. Tyagi SC, Simon SR (1993): Regulation of neutrophil elastase activity by elastin-derived peptide. J Biol Chem 268:16513–16518.
33. Senior RM, Griffin GL, Eliszar CJ, Shapiro SD, Goldberg GI, Welgus HG (1991): Human 92- and 72-kilodalton type IV collagenases are elastases. J Biol Chem 266:7870–7875.
34. Ghuysen-Itard AF, Robert L, Jacob MP (1992): Effect of elastin peptides on cell proliferation. C R Acad Sci III 315:473–478.
35. Herron GS, Werb Z, Dwyer K, Banda MJ (1986): Secretion of metalloproteinase by stimulated capillary endothelial cells. J Biol Chem 261:2810–2813.
36. Montesano R, Vassalli JD, Baird A, Guillemin A, Orci L (1986): Basic fibroblast growth factor induces angiogenesis in vitro. Proc Natl Acad Sci U S A 83:7297–7301.
37. Ladoux A, Frelin C (1993): Hypoxia is a strong inducer of vascular endothelial growth factor mRNA expression in the heart. Biochem Biophys Res Commun 195: 1005–1010.

38. Chua CC, Chua BHL, Zhao ZY, Krebs C, Diglio C, Perrin E (1991): Effect of growth factor on collagen metabolism in cultured human heart fibroblasts. Connect Tissue Res 26:271–281.
39. Tyagi SC, Meyer L, Kumar SG, Schmaltz RA, Reddy HK, Voelker DJ (1996): Induction of tissue inhibitor of metalloproteinase and its mitogenic response to endothelial cells in human atherosclerotic and restenotic lesions. Can J Cardiol 12:353–362.
40. Wach H, Seyama Y, Yamashita S, Suganami H, Uemura Y, Okamoto K, Yamada H, Tajima S (1995): Stimulation of cell proliferation and autoregulation of elastin expression by elastin-peptide VPGVG in cultured chick vascular smooth muscle cells. FEBS Lett 368:215–219.
41. Senior RM, Griffin GL, Mecham RP (1980): Chemotactic activity of elastin derived peptides. J Clin Invest 66:859–862.
42. Szendroi M, Meimon G, Bakala H, Robert L, Godeau G, Hornebeck W (1984): On the presence of a metalloproteinase in human skin fibroblasts that degrades human elastic fiber system. J Invest Dermatol 83:224–228.
43. Cohen JR, Sarfati I, Danna D, Wise L (1992): Smooth muscle cell elastase, atherosclerosis, and abdominal aortic aneurysma. Ann Surg 216:327–330.
44. Tyagi SC, Kumar SG, Alla SR, Reddy HK, Voelker DJ, Janicki JS (1996): Extracellular matrix regulation of metalloproteinase and antiproteinase in human heart fibroblast cells. J Cell Physiol 167:137–147.
45. Carroll SM, White FC, Roth DM, Bloor CM (1993): Heparin accelerates coronary collateral development in a porcine model of coronary artery occlusion. Circulation 88:198–207.
46. Kon K, Fujiwara T (1994): Transformation of fibroblasts into endothelial cells during angiogenesis. Cell Tissue Res 278:625–628.
47. Hoover RL, Rosenberg R, Haering W, Karnovsky MJ (1980): Inhibition of rat artrial smooth muscle cell proliferation by heparin II: In vitro studies. Circ Res 47:578–583.
48. Williams DO, Amsterdam EA, Miller RR (1988): Functional significance of coronary collateral vessels in patients with acute myocardial infarction: Relation to pump performance, cardiogenic shock and survival. Am J Cardiol 61:345–351.
49. Epstein S (1988): Influence of stenosis severity on coronary collateral development and importance of collaterals in maintaining left ventricular function during acute coronary occlusion. Am J Cardiol 61:866–868.
50. Faury G, Ristori MT, Veretti J, Jacob MP, Robert L (1995): Effect of elastin peptide on vascular tone. J Vasc Res 32:112–119.
51. Wight TN, Kinesella MG, Qwarnstrom EE (1992): The role of proteoglycans in cell adhesion, migration, and proliferation. Curr Opin Cell Biol 4:793–801.