Expression, Regulation, and Function of IGF-1, IGF-1R, and IGF-1 Binding Proteins in Blood Vessels

Patrice Delafontaine, Yao-Hua Song, Yangxin Li

Abstract—The vascular insulin-like growth factor (IGF)-1 system includes the IGFs, the IGF-1 receptor (IGF-1R), and multiple binding proteins. This growth factor system exerts multiple physiologic effects on the vasculature through both endocrine and autocrine/paracrine mechanisms. The effects of IGF-1 are mediated principally through the IGF-1R but are modulated by complex interactions with multiple IGF binding proteins that themselves are regulated by phosphorylation, proteolysis, polymerization, and cell or matrix association. During the last decade, a significant body of evidence has accumulated, indicating that expression of the components of the IGF system are regulated by multiple factors, including growth factors, cytokines, lipoproteins, reactive oxygen species, and hemodynamic forces. In addition, cross-talk between the IGF system and other growth factors and integrin receptors has been demonstrated. There is accumulating evidence of a role for IGF-1 in multiple vascular pathologies, including atherosclerosis, hypertension, restenosis, angiogenesis, and diabetic vascular disease. This review will discuss the regulation of expression of IGF-1, IGF-1R, and IGF binding proteins in the vasculature and summarize evidence implicating involvement of this system in vascular diseases. (Arterioscler Thromb Vasc Biol. 2004;24:1-10.)

Key Words: insulin-like growth factor-1 ■ insulin-like growth factor binding proteins ■ blood vessels ■ signaling pathways ■ vascular diseases

The insulin-like growth factors (IGFs) are synthesized by almost all tissues and are important mediators of cell growth, differentiation, and transformation.1 Because of the wide range of their biologic effects and their therapeutic potential, the IGFs have become the focus of research by an increasing number of investigators. This review will focus on the expression, regulation, and function of IGF-1, IGF-1 receptors (IGF-1Rs), and IGF-1 binding proteins (IGFBPs) in blood vessels.

IGF-1 is the product of the IGF-1 gene, which has been mapped to chromosome 12 in humans and chromosome 10 in mice.2 The mammalian gene consists of at least 6 exons, and transcription results from at least 2 transcription start sites located on exon 1 and exon 2.2 Additional complexity results from the presence of distinct carboxyterminal E domains of IGF-1 (Ea and Eb variants). Exon 1 and Ea-containing transcripts are expressed ubiquitously, whereas exon 2 and Eb transcripts are expressed more specifically in the liver.2 IGF-1 has a fundamental role in both prenatal and postnatal development and exerts all of its known physiologic effects by binding to the IGF-1R,3 and its effects are modulated by multiple IGFBPs.4 Circulating IGF-1 is generated by the liver under the control of growth hormone. The binding of growth hormone with its hepatic receptor stimulates expression and release of IGF-1 peptide in the circulation, which has high affinity for IGFBPs, and represents the endocrine form of IGF-1.2,4 In addition to the liver, many other organs produce IGF-1, which has a lower affinity for IGFBPs, representing the autocrine and paracrine form of IGF-1.2,4

The human IGF-1R is the product of a single-copy gene located on chromosome 15 and is ubiquitously expressed.2 The mature receptor is a tetramer consisting of 2 extracellular α-chains and 2 intracellular β-chains.1 The β-chains include an intracellular tyrosine kinase domain that is thought to be essential for most of the receptor’s biologic effects.2 IGF-1R signaling involves autophosphorylation and subsequent tyrosine phosphorylation of Shc and insulin receptor substrate (IRS)-1, -2, -3, and -4.3 IRS serves as a docking protein and can activate multiple signaling pathways, including phosphatidylinositol 3-kinase (PI3K), Akt, and mitogen-activated protein kinase (MAPK).3-5 The activation of these signaling pathways induces differential biologic actions of IGF-1, including cell growth, differentiation, migration, and survival? (Figure 1). “Cross-talk” between IGF-1 and other growth factors makes the IGF-1 signaling cascade more complicated.3-9

The IGFBP family has at least 6 members, which serve as transporter proteins and as storage pools for IGF-1. The expression of IGFBPs are tissue- and developmental stage-specific, and the concentrations of IGFBPs in different body compartments are different.10 The functions of IGFBPs are regulated by phosphorylation, proteolysis, polymerization, and cell or matrix association of the IGFBP.10 All 6 IGFBPs
have been shown to inhibit IGF-1 action, but IGFBP-1, -3, and -5 are also shown to stimulate IGF-1 action. Some of IGFBPs’ effects might be IGF-1 independent. Whereas the IGFBPs consistently have extremely high affinity for IGF-1, the N-terminally truncated des-IGF-1 and a variety of IGF-1 analogues have markedly reduced affinity for IGFBPs but retain normal affinity for IGF-1R.

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IGF-1 and VSMCs
IGF-1 is synthesized and secreted by cultured vascular smooth muscle cells (VSMCs). There are 3 primary mRNA transcripts, 0.9 to 1.2 kb, 1.7 kb, and 7.5 kb, and IGF-1 gene expression in VSMCs is regulated by several factors (Table 1). Thrombin and serum deprivation, tumor necrosis factor-α, and estrogen downregulate IGF-1 mRNA and protein levels. In contrast, reactive oxygen species (ROS) increase IGF-1 mRNA and protein in rat VSMCs. Angiotensin II (Ang II) has been reported to both increase IGF-1 mRNA and protein, and decrease IGF-1 transcripts in rat VSMCs. Platelet-derived growth factor (PDGF) also has been reported to both increase and decrease IGF-1 mRNA levels. Native LDL dose-dependently increases IGF-1 mRNA, but the same doses of oxidized LDL (oxLDL) significantly reduce IGF-1 mRNA and protein expression.

IGF-1 is a potent mitogen and antiapoptotic factor for VSMCs, and it also stimulates migration of VSMCs. Thus, potential reductions in IGF-1 effects might be beneficial in certain pathologic conditions, such as hypertension and the early stages of atherosclerotic plaque formation characterized by hypertrophy/hyperplasia of VSMCs, but detrimental in...
other conditions in which loss of VSMCs contributes to the disease process, such as destabilization of atherosclerotic plaques. The ability of IGF-1 to stimulate the G1-to-S phase progression is important for mitogenic effects of other growth factors. Thus, anti–IGF-1 antisera inhibits Ang II and PDGF-induced VSMC growth. IGF-1 can reduce oxLDL-induced mitochondrial dysfunction, cytochrome c release, and apoptosis in VSMCs and can also inhibit TNF-α–induced caspase-3 activation and apoptosis of VSMCs. Targeted expression of IGF-1 to smooth muscle by an α-actin promoter in transgenic mice resulted in smooth muscle hyperplasia in arteries, veins, and other smooth muscle–rich tissues and corresponding organ hypertrophy and notably increased aortic medial area and thickness. These findings support a central role of IGF-1 in mediating VSMC growth and survival.

IGF-1R and VSMCs

The IGF-1R is expressed on VSMCs and regulated by several factors (Table 1) via multiple signaling pathways. Ang II–induced upregulation of IGF-1R mRNA and protein is mediated by the activation of a tyrosine kinase, the transcription factor nuclear factor (NF)-κB, and ROS and was shown to be protein kinase C independent. Basic fibroblast growth factor–induced upregulation of IGF-1R mRNA is mediated by the transcription factors STAT1, STAT3, and the Janus kinase-2 kinase. The Ras-Raf–MAPK kinase pathway was shown to be required for effects of both growth factors. Thrombin-induced upregulation of IGF-1R mRNA and protein levels in VSMCs was protein tyrosine kinase and NAD(P)H oxidase dependent. In contrast, protein kinase C, epidermal growth factor receptor kinase, Janus kinase-2 kinase, and Src kinase were not involved in this process. Estrogen-induced downregulation of IGF-1R mRNA and protein in rat aortic VSMCs was mediated by the inhibition of SP-1 binding to the IGF-1R promoter. OxLDL significantly reduced IGF-1R mRNA and protein expression, but the mechanism was not clear.

IGF-1R density is a critical determinant of VSMC growth response. Thus, the upregulation of IGF-1R expression by Ang II, basic fibroblast growth factor, and thrombin on VSMCs is critical for their mitogenic effects. The down-regulation of IGF-1R expression by oxLDL is critical for oxLDL-induced VSMC apoptosis. Recently, we have reported that overexpression of IGF-1R by an adenovirus prevented oxLDL–induced apoptosis of human VSMCs.

The function of IGF-1 is also regulated by cross-talk between IGF-1R and other receptors, including integrin receptors. Ligand occupancy of the αVβ3 integrin influences the recruitment of the phosphatase SHP-2 to the IGF-1R receptor. Blocking ligand occupancy of αVβ3 results in premature recruitment of SHP-2 to the IGF-1R receptor and reduces IGF-1R signaling. Therefore, αVβ3 integrin antagonists block IGF-1–induced DNA synthesis, VSMC migration, and IGF-1R–mediated intracellular signaling. Cross-talk between IGF-1R and other growth factors has implications for understanding the requirement for IGF-1R signaling in mitogenic effects for other growth factors.

IGFBPs and VSMCs

The expression and secretion of IGFBPs in VSMCs are species specific. Human VSMCs express mRNAs for IGFBPs -2 through -6, and corresponding proteins are detected in conditioned medium, with the exception of IGFBP-3. In addition, low-molecular-mass immunoreactive degradation products for IGFBP-2 and -4 are also found. Bovine aortic SMCs express predominantly IGFBP-3 and -4, rat VSMCs express predominantly IGFBP-2 and -4, and porcine aortic SMCs express BP-2, -4, and -5. The expression of IGFBPs in VSMCs is regulated by many factors, including platelet-derived growth factor, fibroblast growth factor, transforming growth factor-β, and IGF-1 (Table 1), and the regulation is species specific and dependent on the specific form of IGFBPs. In rat aortic VSMCs, Ang II, thrombin, and ROS reduce IGFBP-4 in conditioned medium, and IGF-1 and IGF-II induce IGFBP-4 proteolysis in these cells. Serum starvation significantly lowered the mRNA levels of IGFBP-2 to IGFBP-6 mRNA. In contrast, TNF-α markedly increased IGFBP-3 mRNA and protein, and native LDL and oxLDL significantly increased IGFBP-2 and IGFBP-4 protein levels in rat VSMCs. Gustafsson et al reported that IGF-1 increases BP-2 and BP-4 mRNA in rat VSMCs, whereas Cohick et al reported that IGF-1 affected neither BP-2 nor BP-4 mRNA levels in porcine VSMCs but decreased IGFBP-4 protein in conditioned medium of these cells. IGF-1 transcriptionally regulated IGFBP-5 in porcine aortic VSMCs. Targeted overexpression of IGF-1 in smooth muscle was not associated with changes in BP-4 and BP-5 mRNA or protein levels, indicating that long-term overexpression of IGF-1 in vivo cannot further increase BP-5 gene expression, contrary to short-term in vitro effects. Studies indicate that local IGFBPs are important determinants of VSMC responses to IGF-1. IGFBP-2 and IGFBP-4 were found to inhibit IGF-1–stimulated DNA synthesis and VSMC migration. IGFBP-5 had an inhibitory effect on IGF-1–stimulated DNA synthesis, but it strongly potentiated IGF-1–induced VSMC migration. Duan and Clemons also demonstrated that BP-4 inhibits IGF-1–stimulated DNA synthesis, whereas BP-5 has potentiating effects in VSMCs.

The functions of IGFBPs in VSMCs are also regulated by phosphorylation, proteolysis, polymerization, and matrix association of the IGFBP. Posttranslational phosphorylation of IGFBPs significantly increases their affinity for IGF-1 and can therefore suppress the function of IGF-1 at the cellular level. However, proteolysis or polymerization of IGFBPs or binding to extracellular matrix results in reduction or loss of IGF-1 binding to IGFBPs, thus increasing the binding of IGF-1 to IGF-1R and the activity of IGF-1. The polymerization of IGFBP-1, through a reduction in binding affinity, leads to loss of IGFBP-1’s ability to inhibit IGF-1–stimulated protein synthesis in VSMCs. Imai et al have shown that a protease-resistant form of IGFBP-5 is an inhibitor of IGF-1 actions on porcine SMCs in culture. Parker et al have shown that binding of IGFBP-5 to porcine SMC extracellular matrix increases the cellular response to IGF-1. BP-5 is cleaved by physiologic concentrations of thrombin, leading to increased free IGF-1 levels, which contribute to...
thrombin’s mitogenic effects. Targeted expression of a protease-resistant BP-4 mutant in smooth muscle of transgenic mice results in BP-4 stabilization and smooth muscle hypertrophy, suggesting that IGF-1–induced hypertrophy is regulated by BP-4 proteolysis. The zinc-binding metalloproteinase pregnancy-associated plasma protein A (PAPP-A) has been identified as a major IGFBP-4 protease and is expressed in VSMCs. All 6 IGFBPs have been shown to regulate IGF-1 actions; however, the mechanisms are different. IGFBP-3 is unique in combining with the acid-labile subunit and is the primary stabilizer of circulating IGF-1. IGFBP-1, IGFBP-2, and IGFBP-4, also found in the bloodstream, can cross endothelial barriers and might transport IGF-1 from blood to peripheral tissue. BP-4 is the most abundant IGFBP expressed in the rat artery wall in vivo and is the dominant IGFBP secreted by rat VSMCs in vitro. IGFBPs also mediate IGF-independent biologic effects. IGFBP-1 stimulates Chinese hamster ovary cell migration via an IGF-independent mechanism involving binding to integrin receptors, whereas IGFBP-3 and IGFBP-5 might have specific cell-surface receptors with serine kinase activity. Using a non–IGF-binding IGFBP-5 mutant and an IGF-1 neutralizing antibody, Hsieh et al demonstrated that IGFBP-5 stimulates VSMC migration by interacting with cell-surface heparan sulfate proteoglycans, which is an IGF-independent effect. Interestingly, the decrease of SMC mass in BP-4 transgenic mice occurred without changes in IGF-1 abundance or gene expression, suggesting that the inhibitory action of BP-4 on SMC mass might occur through an IGF-independent mechanism.

IGF-1, IGF-1R, and IGFBPs in ECs

The expression of IGF-1 in endothelial cells (ECs) is low, which might reflect to a significant extent IGF-1 sequestered from serum. Both macrovessel and microvessel ECs express IGF-1R. Similarly, macrovessel and microvessel bovine ECs express IGFBP-2 through BP-6 mRNA, although microvessel cells secrete predominantly BP-2 and BP-3, whereas macrovessel ECs secrete mainly IGFBP-3 and BP-4. The expression of components of the IGF system in ECs is regulated by various conditions and growth factors, including vascular origin, cell density, hypoxia, transforming growth factor-β1, vascular endothelial growth factor, thrombin, transforming growth factor, TGF, transforming growth factor. See text and the footnote to Table 1 for explanation of other abbreviations.

### Regulation and Role of IGF-1, IGF-1R, and IGFBPs in Vascular Pathologic States

**Atherosclerosis**

Atherosclerosis, the leading cause of mortality in the Western world, is a complex disease involving multiple cell type, including circulating, inflammatory, and progenitor cells, and multiple cell types within the arterial wall. SMC proliferation and migration contribute to the development of atherosclerotic plaque; however, SMC apoptosis is a hallmark of advanced atherosclerotic plaque and particularly unstable plaque that is predisposed to rupture and/or erosion, leading to acute coronary events. Thus, the IGF-1 system might contribute to the balance between the death and survival of VSMCs in atherosclerotic lesions (Figure 2). Grant et al have reported that IGF-1, IGF-1R, and IGFBP-1 through IGFBP-5 were not detected in SMCs of...
normal coronary arteries but were markedly increased in atherectomy specimens. However, IGF-1 and IGF-1R expression is reduced in advanced plaques, and this is consistent with the increased apoptotic rates of VSMCs from atherosclerotic plaques, which also secrete higher levels of IGFBPs. OxLDL is crucially important in the pathogenesis of atherosclerosis and potentially in the depletion of VSMCs, contributing to plaque destabilization, and its ability to decrease IGF-1/IGF-1R expression in VSMC might be an important mechanism leading to VSMC loss. The ability of TNF-α to Reduce IGF-1 and to increase IGFBP-3 could also be important for plaque destabilization. An αvβ3 integrin antagonist reduces atherosclerotic lesion size in pigs and inhibits IGF-1 signaling. It is important to note that PAPP-A, an IGFBP-4 protease, has been reported to be present in unstable but not stable plaques, and its circulating levels are elevated in acute coronary syndromes. A potential proinflammatory effect of IGF-1 that could promote early atherosclerosis has been suggested by Che et al, who demonstrated that IGF-1 enhanced TNF-α-induced adhesion molecule expression in cultured, bovine ECs.

Although reported changes of circulating IGF-1 and IGFBPs in atherosclerotic vascular disease are not consistent, of particular interest is the recent report that individuals with low circulating IGF-1 levels and high IGFBP-3 levels had a significantly increased risk of developing atherosclerosis and ischemic heart disease during a 15-year follow-up period. Janssen et al have reported that high fasting serum free IGF-1 levels are associated with a decreased prevalence of coronary artery disease, whereas high fasting IGFBP-1 levels are associated with a more favorable cardiovascular profile. Furthermore, a polymorphism of the IGF-1 gene associated with lower circulating IGF-1 levels has been demonstrated to be related to 2 early markers of atherosclerosis, namely, carotid intima-media thickness and aortic pulse wave velocity.

Restenosis

Restenosis remains a major clinical problem after percutaneous coronary interventions and results from vessel recoil, neointimal proliferation, and early thrombus formation. Neointimal proliferation is the critical determinant of in-stent restenosis. Multiple growth factors and cytokines are involved in the restenotic process, including IGF-1. Thus, IGF-1 and IGF-1R mRNA levels are reported to be increased in synthetic VSMCs from de novo and restenotic coronary plaques compared with normal coronary arteries. Moreover, IGF-1 is upregulated in rat aortas after balloon denudation, whereas IGF-1R is downregulated. Transgenic mice with IGF-1 overexpression show VSM hyperplasia and mice with paracrine overproduction of IGFBP-4 developed smooth muscle hypoplasia consistent with growth-inhibitory effects of IGFBP-4. IGFBP-4 protease (ie, PAPP-A) expression and proteolytic activity are reportedly increased in VSMCs after injury, suggesting a role for this protease in mediating increases in bioactive IGF-1. Thus, IGF-1 likely contributes to the proliferation and migration of VSMCs that are characteristic of restenosis.

Animal studies show that IGF-1 inhibitors, including angiopentin and octreotide, prevent VSMC proliferation and neointimal formation. However, clinical trials show that octreotide has no benefit and the effects of angiopentin on restenosis are equivocal. This discrepancy could be due to different doses and treatment regimes. It is important to note that an inhibitory stable D-peptide analogue of IGF-1 inhibits VSMC proliferation after rat carotid artery balloon injury, consistent with a role for IGF-1 in the restenotic process.

Angiogenesis

Angiogenesis occurs during normal wound healing and atherogenesis and is regulated by many growth factors, including IGF-1. IGF-1 stimulates vascular EC migration and tube formation and promotes rat aortic angiogenesis in vitro. IGF-1 is important for promoting retinal angiogenesis, and an IGF-1R antagonist suppresses retinal neovascularization in vivo by inhibiting vascular endothelial growth factor signaling. Recombinant IGF, as well as the local delivery of an IGF-1 adenoviral vector, stimulates angiogenesis and neovascularization. Increased monocyte expression of IGF-1 in ischemic tissue could contribute to the angiogenic process.

Diabetes and Hyperinsulinemia

Studies indicate that IGF-1 might be a potential mediator of vascular growth responses in insulin-deficient diabetes and in hyperinsulinemic states. The actions of the IGF-1 system in local tissues might be modified when glucose concentrations are increased. Insulin increases IGF-1 expression in rat aorta, indicating that hyperinsulinism might favor atherogenesis via enhanced expression of IGF-1 in the vessel wall. In the insulin-deficient diabetic rat, IGF-1 mRNA levels are markedly decreased in the heart, skeletal muscle, and aorta, which might explain the observation that DNA synthesis after balloon-injury of the aorta is either decreased or unchanged in diabetes.
Hyperglycemia. Has been reported to induce insulin resistance and expression. In streptozotocin-diabetic rats, aortic IGF-1 expression was unaffected; in contrast, aortic IGF-1 protein expression was increased, and relaxation caused by IGF-1 was significantly greater in aortic strips from streptozotocin-induced diabetic rats than in age-matched, control rats. Insulin treatment ameliorated endothelial dysfunction in these rats and further increased IGF-1R expression.

One consequence of long-term hyperglycemia is the formation of advanced glycation end-products (AGEs); the accumulation of AGEs in the vessel wall could play an important role in the pathogenesis of diabetic vascular complications, including atherosclerosis. AGEs enhance proinflammatory pathways and atherosclerotic lesion development in diabetic apolipoprotein E-null mice. AGE induction of IGF-1 synthesis in human monocytes could play a role in hyperglycemia-induced vascular proliferative changes.

Although VSMCs and ECs express both the insulin receptor and IGF-1R, the vasodilation induced by insulin might be mediated primarily via its stimulatory effects on the IGF-1R. In streptozotocin-diabetic rats, aortic IGF-1 mRNA expression was unaffected; in contrast, aortic IGF-1 receptor mRNA was increased, and relaxation caused by IGF-1 was significantly greater in aortic strips from streptozotocin-induced diabetic rats than in age-matched, control rats. Insulin treatment ameliorated endothelial dysfunction in these rats and further increased IGF-1R expression.

The role of the IGF-1 system in diabetic retinopathy is unclear. IGF-1 mRNA levels are substantially lower in the human and rat diabetic retina, whereas IGF-1R activation and signaling are not affected after 5 months of streptozotocin-induced diabetes in rats. In human retina ECs, long-term exposure to high concentrations of glucose was able to reduce IGF-1-induced mitogenesis by decreasing the stimulatory IGFBP-2, -3, and -5 levels, leaving the concentration of the inhibitory IGFBP-4 constant.

It is of note that hepatic IGF-1 gene deletion induces insulin resistance in mice, and low circulating IGF-1 is associated with an increased risk for developing insulin resistance in humans. IGF-1 therapy can improve insulin sensitivity. Overexpression of IGFBP-1 in transgenic mice has been reported to induce insulin resistance and hyperglycemia.

### Table 3. Alterations of the IGF-1 System and Pathophysiology of Vascular Diseases

| Atherosclerosis | 1. VSMC proliferation and migration are induced by IGF-1. Decreased expression of IGF-1 and IGF-1R in intima potentially contribute to plaque instability. Increased IGF-1 mRNA and protein expression in hypertensive rat aorta. The vasoactive effects of IGF-1 indicate that IGF-1 can control blood pressure and regional blood flow via NO. Short-term injection of IGF-1 decreased mean arterial pressure, and this effect was inhibited by preinfusion of an NO inhibitor, indicating that the decrease in blood pressure in response to IGF-1 is mediated by NO. A significant elevation of arterial pressure was also observed in mice homozygous for a site-specific insertion mutation in exon 3 of IGF-1. Peripheral resistance and systolic blood pressure were increased in liver-specific IGF-1 knockout mice. In spontaneously hypertensive rats, IGF-1-induced vasorelaxant effects were impaired before the onset of hypertension, indicating that this effect could play a causative role in the development of hypertension. It is of note that smooth muscle–targeted overexpression of IGF-1 results in enhanced vascular contractility, possibly via regulation of contractile protein expression.

### Summary and Perspectives for Future Research
IGF-1 exerts multiple physiologic effects on the vasculature, including proliferative, hypertrophic, survival, vasomotor, and metabolic effects. The expression of IGF-1, IGF-1R, and IGFBPs in blood vessels is regulated by multiple factors,
including growth factors, cytokines, lipoproteins, ROS, and hemodynamic forces. Cross-talk between the IGF-1 system and other growth factors at the level of the ligand receptor and at the level of postreceptor signaling pathways has important implications for understanding potential involvement of the IGF system in vascular diseases. Despite the technical challenges in successfully using the Cre-lox and transgenic approaches with cell type–specific promoters, the overexpression or downregulation of IGF-1, IGF-1R, and IGFBPs in selected tissues of transgenic or knockout models will be a promising strategy to reveal the endocrine paracrine function of the IGF-1 axis in different pathophysiologic conditions. Future directions for research include addressing the mechanisms whereby IGF-1 interacts with specific form of IGFBPs, elucidation of the IGF-1–independent function of IGFBPs, and the physiologic role of specific IGFBP proteases. Undoubtedly, insights gained from basic research will lead to novel and pertinent clinical research targeted at prevention and therapy of vascular diseases.145–150

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