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IGF-1 and Cardiovascular Disease

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Abstract

Atherosclerosis is an inflammatory arterial pathogenic condition, which leads to ischemic cardiovascular diseases, such as coronary artery disease and myocardial infarction, stroke, and peripheral arterial disease. Atherosclerosis is a multifactorial disorder and its pathophysiology is highly complex. Changes in expression of multiple genes coupled with environmental and lifestyle factors initiate cascades of adverse events involving multiple types of cells (e.g. vascular endothelial cells, smooth muscle cells, and macrophages). IGF-1 is a pleiotropic factor, which is found in the circulation (endocrine IGF-1) and is also produced locally in arteries (endothelial cells and smooth muscle cells). IGF-1 exerts a variety of effects on these cell types in the context of the pathogenesis of atherosclerosis. In fact, there is an increasing body of evidence suggesting that IGF-1 has beneficial effects on the biology of atherosclerosis. This review will discuss recent findings relating to clinical investigations on the relation between IGF-1 and cardiovascular disease and basic research using animal models of atherosclerosis that have elucidated some of the mechanisms underlying atheroprotective effects of IGF-1.

1. Introduction

<Mechanisms of Atherosclerosis: Updates>

Atherosclerosis is a pathogenic condition characterized by the focal inflammatory thickening of arterial walls. It is the primary cause of cardiovascular diseases (CVDs), such as ischemic heart disease, stroke, and peripheral artery diseases. As CVDs are the leading cause of death worldwide [1], there have been significant continuing efforts to develop therapeutic strategies directly addressing atherosclerotic lesions and preventing adverse events. Nonetheless, development of new drugs has been challenging [2], and current options for medical treatment are still restricted to preventative lifestyle changes, lipid lowering therapy and control of risk factors such as hypertension and glycemic control.

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Conflict of Interest Statement

We have no conflict of interest to declare.

Atherosclerosis is a multifactorial disease [3–5] and our understanding of its pathogenesis has advanced significantly over the past decade. By the early 2000s, major working hypotheses proposed as mechanisms of atherogenesis included the "*response-to-retention hypothesis*" [6], and the "*oxidative modification hypothesis*" [6]. These hypotheses stated that lesions are initiated when there is subendothelial retention of lipids (low-density lipoproteins) which are modified (e.g. aggregated, oxidized) to be biologically active. Modified lipids elicit subintimal infiltration of macrophages, which scavenge modified lipids to become lipid-laden macrophages (i.e. foam cells), thereby establishing an early lesion (i.e. fatty streak). Modified lipids and chemokines/cytokines from pro-inflammatory cells induce de-differentiation and migration of medial smooth muscle cells (SMCs) into the intima. The undifferentiated SMCs ("synthetic phenotype" SMCs, as opposed to differentiated "contractile phenotype" SMCs) proliferate and deposit matrix proteins leading to neointimal thickening. Under highly inflammatory and oxidative conditions, macrophages and SMCs may undergo cell death, resulting in necrotic core formation and ultimately causing plaque vulnerability.

The concept of "*endothelial dysfunction*" that precedes atherosclerosis development is now widely accepted [7] and further substantiated by recent findings. In addition to its classical roles in vasomotor activity, thrombosis and fibrinolysis, blood-tissue exchange, and angiogenesis, the endothelium is now recognized as a regulatory hub orchestrating vascular homeostasis [8], as a sensor and principal mediator of fluid shear stress to the arterial wall [8–10], as a regulator of proinflammatory cell recruitment and invasion [8, 11, 12], and as an integral component of mechanisms of arterial stiffness [13, 14].

New insights are also emerging about the potential roles of SMCs in atherosclerosis. The term "phenotypic switch of SMCs" used to refer to a shift of SMC phenotype from fully differentiated "contractile" state to de-differentiated "synthetic" state. However rigorous investigations in the past decade revealed that the fate of arterial SMCs under the atherogenic microenvironment is more diverse, ranging from a mesenchymal stem cell-like phenotype to a macrophage-like phenotype [15]. More than 80% of SMC-derived cells in advanced plaques do not express some or all of SMC-markers but express markers of mesenchymal stem cells [16] or even macrophages [16–18]. Vice versa, myeloid cells can express SMC-markers [19, 20]. 10–15% of α-smooth muscle actin-positive cells within an advanced plaque are derived from myeloid cells [21]. Macrophage-like cells derived from SMCs are highly pro-inflammatory, limited in phagocytic capacity, and prone to cell death [15], which may ultimately promote atheroma formation.

The significance of SMC proliferation in terms of the development of pathogenic lesions is under debate. Pathologic intimal thickening (PIT) plays an important role in the initiation and progression of atheroma formation and is distinct from non-atherosclerotic intimal thickening, which is referred to as diffuse intimal thickening (DIT) and adaptive intimal thickening (AIT, or also called eccentric intimal thickening) [22–25]. DIT has been recognized for decades [26]. DIT consists of SMCs and matrix proteins without lipid accumulation and is widespread in the arterial bed in humans. In fact, it was reported that 100 % of humans have coronary arterial DIT by 3-months of age [27, 28]. AIT is a focal thickening exceeding the thickness of DIT and frequently develops at branch-points and

areas of turbulent blood flow [29], sites where atherosclerotic lesions frequently develop [30]. However there is no clear distinction between AIT and DIT in terms of their cellular or noncellular composition; they often continuously develop on a span of the arterial bed. DIT and AIT are considered to result from a physiological response to blood flow and tensile stress [22–25]; nevertheless, they may make a transition to PIT through poorly understood processes, leading to subsequent atheroma formation. Indeed, recent findings suggest that the transition of DIT/AIT to PIT involves modification of extracellular matrix proteins and deposition of non-cellular blood components in the intima [31, 32], influx of pro-inflammatory cells, and SMCs' phenotypic switch and cell death [22–25]. It is noteworthy that most acute coronary events are related to rupture or erosion of atherosclerotic plaques that are not hemodynamically significant [33]. Thus one can speculate that early transition of AIT/DIT to PIT may contribute to development of non-obstructive but clinically significant (i.e. unstable) atherosclerotic lesions.

Macrophages play a key role in the pathophysiology of atherosclerosis, and recent findings indicate that macrophages, similarly to SMC, may undergo a phenotypic switch [15]. Thus a significant number of macrophage marker (e.g. CD68)-positive cells are of SMC origin, and vice versa, macrophages can express SMC markers (e.g. α–smooth muscle actin) [15]. These findings complicate the interpretation of previous studies relying on cell-type "specific" marker expression. A potentially beneficial function of macrophages has been proposed. In the classical "*response-to-retention*" hypothesis, macrophages are part of a tissue repair mechanism and remove lipids that accumulate in the intima. Macrophages also clear up dying cells within plaques via efferocytosis. There is evidence that plaque macrophages are defective in efferocytosis [34], potentially resulting in accumulation of dying/dead cells and necrotic core expansion.

We previously reviewed potential IGF-1 effects on atherosclerotic diseases [35, 36]. We now provide an update on the effects of IGF-1 on atherosclerosis after a decade of significant advances in our understanding of the pathophysiology of atherosclerosis.

<Insulin-like Growth Factor system>

Insulin-like growth factor 1 (IGF-1) is a major regulator of postnatal (prepubertal and pubertal) somatic growth, mediating many of the effects of growth hormone (GH). Circulating levels of IGF-1 reach to their highest at mid-teen years (111–647 ng/mL) and then decline with age. In healthy 40 years old adults, its reference range is approximately 50–65 % lower than its peak range (68–226 ng/mL or 9–30 nM). IGF-1 and its related peptide hormone, insulin, display similar affinities for their respective cognate receptors, but circulating IGF-1 levels are 10-fold or higher. The majority of circulating IGF-1 molecules are complexed with IGF binding proteins (IGFBPs), which hinder IGF-1 from ligating to the insulin receptor or modulate IGF-1 binding to the IGF-1 receptor (IGF1R) [37]. IGF1R is expressed in the three major cell types which are involved in the pathogenesis of atherosclerosis, namely, endothelial cells, macrophages, and SMCs. Biological effects of IGF-1 on cultured vascular endothelial cells, smooth muscle cells, and macrophages have long been described, and more recent in vivo studies have provided insights into the effects of IGF-1 on the pathogenesis of atherosclerosis.

<Growth Factors and Atherosclerosis; Permissive or Preventative?>

Traditionally, the role of growth factors in atherosclerosis has been thought to be permissive, in particular, by stimulating vascular smooth muscle cell (SMC) migration and proliferation, thereby promoting neointima formation [38, 39]. Interestingly, recent reports suggest that some growth factors have atheroprotective effects in animal models of atherosclerosis. Tang et al. [40] tested potential roles of platelet derived growth factor (PDGF)-B on cardiovascular diseases by using a murine model of atherosclerosis, apolipoprotein E-null mice (Apoe-null mice). They transplanted fetal liver cells of Pdgfb/Apoe-dual knockout mice into irradiated Apoe-null mice, therefore the recipient animals lack PDGF-B in circulating cells (such as monocytes and platelets), which are the major source of PDGF in the pathogenesis of atherosclerosis [41]. These animals demonstrated a significant change in atherosclerotic lesion composition, represented by enhanced inflammatory cell infiltration [40]. The same group demonstrated that elimination of PDGF-B in circulating cells or blockade of PDGF receptors delayed but did not inhibit smooth muscle accumulation in lesions, and more importantly, did not influence atherosclerotic burden [42]. These reports suggest a modest contribution of PDGF to atheroprogression but a major inhibitory effect on inflammatory responses and on monocyte accumulation. Transforming growth factor-β (TGF-β) promotes vascular SMC proliferation and matrix protein production (reviewed in [43]). Apoe-null mice with cardiac-specific overexpression of active TGF-β1 develop elevated cardiac and circulating TGF-β levels, less aortic root atherosclerosis, and fewer lesions in the thoracic and abdominal aortae [44]. These plaques were characterized by fewer T lymphocytes, more collagen, less lipid, and lower expression of inflammatory cytokines [44]. We found that elevation of circulating IGF-1 levels (by continuous s.c. infusion, resulted in approximately 2.3-fold elevation of total IGF-1 levels) prevented atherogenesis in Apoe-null mice [45]. These findings suggest preventive or reparative function of certain growth factors, however precise underlying mechanisms are still obscure.

2. IGF-1 and Cardiovascular Disease – Clinical Implications

IGF-1 affects vascular function and atherosclerosis in many ways, including anti-inflammatory and anti-apoptotic actions [46, 47] and stimulation of angiogenesis [48, 49]. It stimulates nitric oxide production in endothelial and vascular smooth muscle cells through activation of nitric oxide synthetase via Akt-catalyzed phosphorylation, thus also playing a role in improved cardiac contractility in exercise training [50]. There is also evidence suggesting that IGF-1 has indirect effects on the cardiovascular system by increasing Insulin sensitivity [51–54].

<Coronary Artery Disease (CAD)>

In healthy subjects a link between low levels of circulating IGF-1 and high prevalence of CAD has been suggested [55, 56]. Patients with acromegaly have a chronic excess of GH and IGF-1, which could lead to acromegalic cardiomyopathy, characterized by biventricular hypertrophy, diastolic and systolic dysfunction, and congestive heart failure[57]. Although Cansu et al. [58] suggested higher subclinical atherosclerosis and left ventricular diastolic dysfunction in a small cohort of patients with acromegaly, and Petrossians et al. [59] reported hypertension in 28.8% of 3173 patients with acromegaly in the LAS database, the

incidence of baseline serious cardiovascular disease was <5% in the same patients [59]. GH deficiency impairs flow-mediated arterial dilation, and thus endothelial NO-dependent vasodilation [60] and increases cardiovascular morbidity and mortality [61–64]. GH supplementation has been reported to improve cardiovascular risk [65]. On the other hand, a small-scale study indicated a lack of evidence of premature atherosclerosis in untreated severe GH deficiency due to a GH-releasing hormone receptor mutation [66], and also a study reported a lack of evidence of elevated mortality due to cardiovascular diseases in Laron syndrome subjects [67]. Of note, a recent meta-analysis failed to confirm a significant positive trend in cardiovascular risk after short and long-term GH supplementation therapy in adult GHD patients [68]. Potentially consistent with these clinical reports, twice-daily sc injection of GH releasing peptide-2 (20 μg/injection, a dose that significantly increases GH and IGF-1 levels [69]) failed to decrease atherosclerosis in Apoe-null mice, even though it successfully elevated serum IGF-1 levels, contradicting atheroprotective effects of IGF-1 [70]. It was speculated that GH-dependent effects may blunt the effect of increased IGF-1 [70].

In possibly the largest observational study on the relation of IGF-1 to CAD in 10,600 coronary-disease free subjects in the PRIME study, Ruidavets et al. [71] found that baseline IGF-1 level was significantly lower in subjects developing an acute coronary syndrome, and that subjects in the highest quartile of IGF-1 distribution had a 55% reduction in the relative risk of developing myocardial infarction [71]. Similarly, De Leronzo et al. [72], in a small study on 36 patients, showed significantly lower IGF-1 level in patients with early-onset CAD [72].

<Stroke>

Johnson et al. [73] suggested a protective effect of IGF-1 against ischemic stroke in the observational Danish study [73]. In contrast, a case-cohort analysis in subjects >65 years old in the Cardiovascular Health Study observational study showed no effect of IGF-1 and IGF Binding Proteins (IGFBPs) on prediction of risk of cardiovascular events or stroke [74]. Saber et al. [75], using observational data from a predominantly Caucasian population of 757 subjects in the Framingham Heart Study, found the lowest incidence of ischemic stroke in patients in the highest quartile of circulating total IGF-1 (232±41.04 ng/ml), especially in diabetics and in patients in the highest waist-hip ratio quartile. They proposed that low circulating IGF-1 level could be related to increased ischemic stroke risk in diabetics and obese individuals, possibly through higher insulin resistance. The study did not find a linear relationship between IGF-1 and stroke and did not measure free IGF-1 and IGFBPs [75].

There are multiple studies on the relationship between IGF-1 and common carotid intima-media thickness (CC-IMT). In a recent study on morbidly obese individuals in a bariatric surgery program, Sirbu et al. [76] suggested that HOMA-IR (a measure of insulin resistance) and total IGF-1 z-score are associated with increased CC-IMT [76]. Similarly, Kawachi et al. [77] showed that IGF-1 levels were correlated with CC-IMT in non-obese individuals, and Splicke et al. [78] showed a positive correlation between serum IGF-1/IGFBP-3 ratio and CC-IMT [77, 78]. Ameri et al. [79] found an interesting negative association of IGF-1 with CC-IMT only in patients in the lowest 25-hydroxyvitamin D quartile in the Baltimore

Longitudinal Study of Aging (BLSA) and the Microalbuminuria: A Genoa Investigation on Complications (MAGIC) study [79]. Abd El-Hafiz et al. [80], in a comparative study of metabolically healthy obese individuals with healthy controls, also suggested that IGF-1 is protective against CC-IMT in the presence of low serum vitamin D [80]. In view of the contradictory data for stroke and CC-IMT Sirbu et al. [76] have postulated that high IGF-1 could stimulate smooth muscle hyperplasia in early atherosclerosis, but promote plaque stability in advanced disease [76, 81]. Muller et al. [82] have also suggested that the variable relation of IGF-1 to stroke and CC-IMT might be explained by the lack of standardization for IGF-1 assays utilized in various studies [82].

<Mortality>

The relation of IGF-1 and long term survival/ mortality has been the subject of much discussion, and seems to be modulated by age, race and gender. Wennberg et al. [83] followed IGF-1 levels in 1618 elderly individuals in the Mayo Study of Aging. Looking primarily at bioavailable IGF-1 (ratio of IGF-1 to IGFBP-3), they reported that males have more rapid age-related decline in IGF-1 compared to females [83]. Sanders et al. [84], in a study of 945 individuals >65 years old in the Cardiovascular Health Study followed over a mean of 11.3 years, found that baseline IGF-1 level <70 ng/ml and higher IGF-1 variability were associated with higher mortality [84]. Similarly, Nillson et al. found higher mortality in hemodialysis patients with lower serum IGF-1 level, modulated by serum albumin.

Schutte et al. [85] preformed a detailed longitudinal observational analysis as part of the PURE study in a high-risk population of black South Africans. They reported that higher IGF-1 levels predicted lower mortality over 5 years after adjustment for IGFBP-3 and was significantly related to maintenance of a normotensive status. Interestingly, they did not observe any association between IGF-1 and CC-IMT, which could be attributed to the different ethnicity of this population compared to previously reported studies [85]. It is also possible that the high risk behavior in the PURE study population, with higher alcohol use, smoking and obesity, could directly lead to lower IGF-1 levels [86].

Burgers et al. [87], in a meta-analysis of 12 studies with 14,906 participants, suggested a U-shaped relationship of IGF-1 with mortality, with increased mortality in subjects with low or high IGF-1 levels compared to mid-centile reference categories [87].

<Peripheral Arterial Disease (PAD)>

There are limited studies on the association of IGF-1 with PAD. Urbaonavicience et al. [88] found higher IGF-1 and lower IGFBP-2 in obese individuals, and reported lower IGF-1 in patients with critical limb ischemia. In the same study, they did not find any improvement in prediction of cardiovascular mortality after adding IGF-1 to a conventional risk model [88]. In a cross-sectional study comparing PAD patients to healthy controls, Brevetti et al. [89] found lower levels of IGFBP-3 in the PAD group, especially in patient with an ankle/ brachial index lower than median. They also demonstrated that a high transfemoral gradient of CRP, a surrogate maker for inflammation, was independently associated with a low transfemoral gradient of IGF-1 and a high transfemoral gradient of IGFBP-3 [89].

<Association of PAPP-A with cardiovascular disease>

Pregnancy-associated plasma protein A (PAPP-A) is a metalloproteinase regulator of insulin-like growth factor bioavailability through cleavage of IGFBP-4, thus releasing bioactive IGF [90]. Hjortbjerg et al. [91], in a longitudinal study of 330 Type I diabetic patients with and without nephropathy followed for >12 years, found higher cardiovascular mortality in patients with high values of the main cleavage products NT-IGFBP-4 and CT-IGFBP-4, but not with PAPP-A [91]. There is active interest in exploring the role of stanniocalcin-2 (STC2), a potent PAPP-A inhibitor, in increasing IGF levels in patients [90, 92].

3. Atheroprotective effects of IGF-1 in animal models of atherosclerosis

<Endocrine IGF-1 and atherosclerosis>

In 2007, we reported that systemic infusion of IGF-1, which doubled circulating IGF-1 levels (665 ng/mL vs. 287 ng/mL in saline infused animals), attenuated atherosclerotic burden in Apoe-null mice [45]. Since this report, we and others have confirmed that systemic IGF-1 levels inversely correlate with atherosclerotic burden [45], consistent with atheroprotective effects of IGF-1. Sivasubramaniyam et al. [93] generated Apoe-null mice with hepatic Jak2 deficiency, which impairs the GH signaling pathway, therefore these mice have significantly lower circulating IGF-1 levels than hepatic Jak2-wild type mice [93]. These animals had significantly accelerated atherosclerosis and the causal relation between low IGF-1 and atherosclerosis was confirmed by supplementing IGF-1 by continuous infusion (at a dose that does not influence glucose tolerance or insulin sensitivity, however reverses GH levels down as low as Jak2-wild type mice [93]) or by overexpression of IGF-1 (by crossbreeding to hepatic IGF-1 overexpression mice in which serum IGF-1 levels were 2.5-fold higher than no-overexpression controls [94]) in hepatocytes of Jak2-deficient mice [93]. Svensson et al. [95] investigated diet-induced fatty streak formation in liver-specific IGF-1 inactivation mice (LI-IGF-1−/− mice), in which the serum IGF-1 level is lower than wild-type control mice by 80 % [95]. This animal model is on a C57Bl/6 background without alterations of genes related to lipid metabolism, thus it is normolipidemic and produces only early stage lesions (fatty streaks), making it a useful model to assess potential effects of endocrine IGF-1 on initiation of plaque development. Intriguingly, they observed that the deficiency of endocrine IGF-1 increased fatty streak formation only in female mice [95]. Increased fatty streak formation was associated with elevated serum cholesterol and signs of systemic inflammation, endothelial activation, and macrophage infiltration in the vascular wall, consistent with atheroprotective effects of endocrine IGF-1. It is noteworthy that the LI-IGF-1−/− mouse produces adult-onset IGF-1 deficiency (i.e. liver-specific Igf1 gene deletion induced at 3 months of age), therefore, the observed atheroprotective effects of IGF-1 are independent of any known developmental effects of IGF-1.

Elevated IGF-1 levels in the circulation not only decreased plaque burden, but also induced phenotypic changes in plaques, represented by a decrease of macrophages, attenuated pro-inflammatory cytokine expression, lowered oxidative stress, less frequent apoptosis, and increased presence of smooth muscle cells and collagen [45, 96, 97]. Vice versa, low levels of circulating IGF-1 in the 6T congenic mouse [98] and in the liver-specific IGF-1 knockout

mouse [93] was associated with enhanced inflammatory phenotype and increased atherosclerotic burden. These observations suggest that IGF-1 may reduce inflammation and promote a more stable plaque phenotype, underscoring IGF-1's therapeutic potential to prevent clinical events caused by plaque vulnerability. For a more comprehensive understanding of potential IGF-1 effects on atherosclerosis, murine atherosclerosis models which carry cell-type specific modifications of the IGF-1 system have been used and provided mechanistic insights for the vascular effects of IGF-1.

<Smooth muscle cells>

In the classical view of mechanisms of atherosclerosis, SMCs were considered to play pro-atherogenic roles. Phenotypic switching of contractile SMCs to synthetic SMCs, which migrate from the media to intima, proliferate, and deposit matrix proteins, was thought to cause plaque thickening [99, 100]. However In the past decade, it has become apparent that SMCs switch to more diverse phenotypes than merely being "synthetic" or "contractile" [15, 101]. Likewise, potential effects of growth factors on SMCs (also on SMC-derived cells and SMC-marker positive cells of other origins) need to be redefined accordingly to an updated view of SMC biology within atherosclerotic lesions. Mechanically induced neointima models (e.g. wire or balloon catheter injury-induced neointima formation) had been used to investigate potential effects of growth factors on fibroproliferative SMCs. However the biology of the neointima (neointimal cells are almost exclusively "synthetic" SMCs without intact endothelial cells covering the lesions) is grossly different from atherosclerotic lesions in humans, as the former lacks involvement of endothelial cells or pro-inflammatory cells, which are essential components in the latter. Therefore, we have avoided inclusion of reports using animal models of injury-induced intimal hyperplasia, which are now considered to represent the pathophysiology of angioplasty-induced restenosis but not atherosclerosis.

IGF-1's effects of promoting vascular SMC migration and proliferation have been proposed as a potential mechanism of restenosis, pulmonary hypertension, and vein graft failure, using animal models of intimal hyperplasia [102–104]. However, investigations on potential effects of IGF-1 on atheroma formation had been lacking. To address the effects of autocrine/paracrine IGF-1 produced by smooth muscle cells on the pathogenesis of atherosclerosis, transgenic mice which overexpress IGF-1 in smooth muscle were created on an Apoe-null background (SMP8-Igf1 mice) [105]. When compared with Apoe-null mice, the SMP8-Igf1 mice developed a comparable plaque burden after 12 weeks on a high fat diet, suggesting that the ability of endocrine IGF-1 to reduce plaque burden [45] was mediated in large part via non-SMC target cells. However, advanced plaques in SMP8-Igf1 mice displayed features of increased plaque stability, including elevated SMC content, increased fibrous cap area, increased collagen levels, and reduced necrotic cores. Of note, the same promoter-driven IGF-1 overexpression in smooth muscle (SMP8-Igf1) substantially promoted neointima formation in an injury-induced arterial intimal hyperplasia model [106], consistent with a significant difference in pathology between arterial intimal hyperplasia and atherosclerosis. The observed consequence of IGF-1-overexpression in SMCs on atherosclerosis is consistent with the earlier studies demonstrating IGF-1 to positively support SMC differentiation [107–109] and elevate matrix protein production. We have subsequently shown that IGF-1 increases collagen synthesis by increasing LARP-6

expression [110]. In both IGF-1 infusion model (mentioned in "*Endocrine IGF-1 and atherosclerosis*" [45]) as well as a smooth muscle cell specific IGF-1 overexpression model, IGF-1 does not increase atherosclerotic burden. However, these studies were done at a 3-month time point of high-fat diet feeding, so potential effects of IGF-1 on early atherosclerotic lesion stage were not determined.

We also evaluated a model of SMC-specific IGF1R loss of function. For this purpose, we cross-bred IGF1R floxed mice to SM22α -CreKI mice, which have Cre recombinase gene knocked-in downstream of the promoter region of SM22α gene, resulting in IGF1R deficiency in SMCs and also in fibroblasts (FB; SM22α-CreKI/IGF1R-flox mice) [111]. IGF1R deficiency caused SMC and FB hypotrophy and decreased expression of collagen. With high-fat diet feeding, SMC-IGF1R deficient mice had increased atherosclerotic burden and inflammatory responses. Also, the IGF1R deficiency decreased plaque SMC content, markedly depleted collagen and increased indices of vulnerability in the plaques [111].

These SMC-selective IGF-1 and IGF1R gain-of-function and loss-of-function models demonstrate that one of the major effects of IGF-1 on SMC is to promote plaque stability by increasing plaque SMC content (via pro-proliferative and anti-apoptotic mechanisms) and plaque collagen matrix. It is interesting to hypothesize that IGF-1 might suppress SMC phenotype switching in favor of preventing atheroprogression, given that IGF-1 supports SMC differentiation [107–109]. Furthermore, SMC-IGF1R deficiency enhanced cell death and inflammation and enlarged necrotic cores in lesions [111]. Blackstock et al. [110] described that IGF-1 positively regulates La ribonucleoprotein domain family member 6 (LARP6), which is an essential regulator of collagen I and III synthesis and fiber assembly, in cultured aortic SMCs and in the aorta of Apoe-null mice, consistent with a novel mechanism whereby IGF-1 increases collagen fibrinogenesis and plaque stability [110].

<Macrophages>

Macrophages are in large part responsible for the development of the inflammatory milieu in plaques. Also, macrophages are major contributors to the accumulation of lipids and the degradation of extracellular matrix; consequently, all of these activities lead to a loss of the structural stability of plaques. Macrophages express IGF-1 and IGF-1R. IGF-1 production by macrophages is often described in the context of tissue regeneration, repair, and fibrosis in an inflamed tissue [112–114], where IGF-1 mediates a transition by enhancing mesenchymal/stromal cell proliferation/migration and matrix deposition. With regard to vascular inflammation, pro-atherogenic factors such as advanced glycosylation end products [115] and TNF-α [116] have been shown to increase IGF-1 synthesis in macrophages.

IGF-1 may act on surrounding cells in a paracrine manner or on macrophage themselves in an autocrine manner. Reports about potential IGF-1 effects on macrophages in the context of atherosclerosis have been conflicting. IGF-1's potentially pro-atherogenic effects have been reported as enhancing chemotactic macrophage migration [117], stimulating tumor necrosis factor-α (TNFα) expression [118], or enhancing low-density lipoprotein (LDL) uptake and cholesterol esterification [119]. On the contrary, IGF-1 was reported to reduce lipid oxidation and foam cell formation by macrophages mediated by 12/15-lipoxygenase [120]. In fact, clinical investigations provide indirect evidence of IGF-1 exerting anti-inflammatory

effects: For instance, administration of the IGF-1 and IGFBP-3 complex attenuated proinflammatory acute phase response in severely burned patients [121, 122]. Of note, some of these in vitro studies used concentrations of IGF-1 well above the physiological range, making it challenging to interpret the results. Interpretation of experiments using IGF-1 on cultured macrophages is often difficult, since experiments are often performed in a serum-containing medium, because of the high sensitivity of macrophages to serum deprivation. Due to serum-derived IGF-1, IGFBPs, insulin, and protein-degrading activity, it is difficult to estimate bioavailability of externally added IGF-1 or insulin. Careful examination of receptor usage (IGF-1R, insulin receptor, or IGF/insulin hybrid receptor) and signaling pathways may be helpful to unravel conflicting previous findings.

Recently, our group assessed a potential direct link between IGF-1 effects on macrophages and atherosclerosis [46] by creating myeloid-specific IGF1R-deficient mice on Apoe-null background (Lyz2-Cre/IGF1R$^{fl/fl}$/Apoe$^{-/-}$ mice). The loss of IGF-1 signaling caused an increase of atherosclerotic burden concomitant with elevated monocyte recruitment to the lesions; moreover, macrophage-IGF1R deficiency induced features of an unstable plaque phenotype [46]. Consistent with these in vivo observations, peritoneal macrophages isolated from this animal model demonstrated enhanced responses to pro-inflammatory stimuli such as interferon-gamma or lipopolysaccharide (i.e. enhanced M1 activation) as well as elevated matrix metalloproteinase production and reduced lipid efflux leading to elevated lipid accumulation [46]. Thus IGF-1 may have a fundamental role in macrophage activation and also modulate atherosclerosis by regulating MMPs expression levels and lipid metabolism.

The downstream signaling pathway from the IGF1R largely coincides with the insulin receptor signaling pathway; moreover, IGF1R and insulin receptor are structurally similar and form a heteromeric tetramer (α+β-subunits of IGF1R and α+β-subunits of insulin receptor; hybrid receptor). These hybrid receptors mediate IGF-1-dependent signaling but not insulin signaling, thus formation of hybrid receptors is inhibitory to insulin effects. Nullifying IGF1R expression could potentially enhance insulin-sensitivity via liberation of insulin receptor subunits to form holoreceptors. Our group investigated IGF1R and insulin receptor expression in mouse peritoneal macrophages and found that both receptors are expressed, however, insulin receptor is expressed predominantly, allowing insulin holoreceptor and IGF-insulin hybrid receptor expression but no IGF-1 holoreceptors [46]. Therefore, it is likely in macrophages that the hybrid receptor mediates IGF-1-dependent signaling, whereas insulin holoreceptor mediates insulin-dependent signaling. Consistently, we observed that the genetic deletion of IGF1R did not influence insulin-induced Akt phosphorylation in macrophages [46], making it unlikely that the elevated atherosclerotic burden is mediated indirectly by altered insulin signaling.

Of note, potential insulin effects on macrophages and atherosclerosis have been a subject of active investigation. In one report, myeloid-specific insulin receptor deletion in Apoe-null mice (Lyz2-Cre/Insr$^{fl/fl}$/Apoe−/− mice) lowered atherosclerotic burden and this was associated with attenuated inflammatory response [123]. On the contrary, insulin receptor-deficient bone marrow transplantation into LDL receptor-null mice caused elevated plaque burden, associated with increased necrotic core size and apoptotic cell numbers [124], mediated by enhanced ER stress and apoptosis of macrophages [124]. Reasons for these

divergence in findings are still obscure; it has been pointed out that the difference in the animal models (Lyz2-Cre mediated floxed-insulin receptor deletion vs. bone marrow transplantation from insulin receptor-deficient mice; Apoe-null vs. LDLR-null), or animal condition (high cholesterol diet vs. high cholesterol+ choline-supplemented diet that is more proinflammatory) may explain the difference [125, 126]. Insulin has been considered pro-inflammatory in macrophages [127, 128] and has been reported to promote foam cell formation [129], in contrast to anti-inflammatory and anti-foam cell formation effects of IGF-1 [46, 120]. Some of above papers do not evaluate receptor usage, even when relatively high dose (100 nM) of insulin had been used. Further studies are necessary to differentiate signaling mechanisms and effects of IGF-1 and insulin on macrophages, in order to elucidate their pathophysiological roles in diseases where chronic inflammation plays a vital role, such as atherosclerosis and diabetes.

<Endothelial cells>

The endothelium is the master regulator of vascular functions such as vascular permeability, vasomotor activity, and pro-or anti-thrombotic activities. The endothelium also plays a leading role in new vessel formation (i.e. angiogenesis) and in establishment of inflammation by recruiting proinflammatory cells via expression of adhesion molecules or chemoattractant factors. Any of these endothelial functions are vital to the integrity of the vasculature, and are therefore important for the pathophysiology of atherosclerosis.

Vascular endothelial cells express IGF1R and thus the endothelium is a target organ of IGF-1[130]. Potential IGF-1 effects on the endothelium have been investigated extensively (reviewed in [130, 131]); however, some of these findings have been conflicting, hence the definite roles of IGF-1 in regulation of endothelial function are still elusive. Elevated vascular permeability is an integral part of the pathogenesis of atherosclerosis and has been recently proposed to be a marker of vulnerable atherosclerotic plaques [132]. It has been reported that IGF-1 supports the endothelial blood-brain barrier function in ischemic brain, reducing permeability and proinflammatory cell infiltration [133]. In a mouse model of renal fibrosis, IGF1R overexpression reduced renal capillary permeability and proinflammatory cell infiltration, vice versa, endothelial specific deficiency of IGF1R lowered endothelial barrier function as seen by increased inflammatory cell infiltration and vascular endothelial-cadherin phosphorylation and increased the fibrosis of kidney disease [134]. On the contrary, IGF-1 was also reported to impair the blood-retinal barrier function by downregulating tight junction proteins via a GSK-3β/CREB dependent mechanism [135, 136]. It has been suggested that in the presence of hyperglycemia the IGF-I/IGF-1R axis stimulates retinal endothelial cell permeability [137]. Reasons for these apparently conflicting observations are not clear. One can speculate that different tissue-derived endothelial cells respond differently to IGF-1, or it is also possible that other factors (e.g. hormones, growth factors, or a specific metabolic condition such as high glucose) influence endothelial cells' response to IGF-1. For instance, hyperglycemia induces the association of integrin-associated protein (IAP) with tyrosine phosphatase non-receptor type substrate-1 (SHPS-1), changing the endothelial cell response to IGF-1 and increasing permeability [138].

Impaired endothelium-dependent vasodilation precedes atherosclerosis development [8, 139, 140]. IGF-1 may promote vasodilation by upregulating eNOS activity in the endothelium and increasing nitric oxide production [141, 142]. In human subjects, low plasma IGF-1 levels are associated with impaired endothelium-dependent vasodilation [143]. In contrast, it has been also shown that IGF1R inhibits insulin-induced eNOS activity, by forming a hybrid receptor (i.e. one combination of IGF-1 alpha-beta subunits complexed with one combination of insulin alpha-beta subunit) [144]. Therefore, a reduction in IGF1R expression levels improved insulin-dependent vasorelaxation [144]; and vice versa, overexpression of IGF1R decreased nitric oxide bioavailability and insulin sensitivity in the endothelium [145]. However there is no evidence as yet that the ability of IGF-1 to stimulate eNOS plays a role in its atheroprotective effects [96]. Of note, IGF1R overexpression promoted endothelial regeneration after denudation, consistent with IGF-1's pro-repair activity in the endothelium [145].

Intriguingly, endothelium-selective overexpression of insulin receptor blunted shear stress induced eNOS activation and elevated superoxide production by NADPH-oxidase, and these two effects combined to decrease NO bioavailability [146], leading to impaired endothelium-dependent vascular relaxation and accelerated atherosclerosis [146]. It can be speculated that the overexpression of insulin receptor could lead to increased abundance of IGF-1/insulin hybrid receptors, thereby potentially enhancing IGF-1 sensitivity in the endothelium. Therefore, the observed consequences may have been caused by enhanced IGF-1-dependent signaling activity in the endothelium. Overall, IGF-1 and insulin signaling pathways are intricately related as are their potential effects on vascular tone.

IGF-1 promotes angiogenesis and nascent vessel formation [141, 147], and also increases endothelialization of denuded artery by promoting endothelial cell proliferation and migration [145]. Promoting re-endothelialization may be beneficial to inhibit restenosis after angioplasty procedures. However, it is unclear whether it also provides benefits in atherosclerosis, since the endothelium layer stays physically intact (however functionally compromised) on atherosclerotic plaques. Angiogenesis or neovascularization in atherosclerotic lesions, which are actually promoted by hypoxia within the lesion, is considered to promote plaque progression and destabilization [148–150]. Endothelial progenitor cells (EPCs) in the circulation or in the vascular wall may contribute to endothelial repair and prevent endothelial dysfunction [151, 152]. Potential effects of IGF-1 on EPC-mediated endothelial repair are unclear. It has been reported that in healthy human subjects or in subjects with GH deficiency the GH/IGF-1 axis positively regulates circulating EPC levels [153–155]. Consistent with these observations in human subjects, IGF-1 administration elevated circulating EPC levels in animal models [45, 153, 156]. More recent reports [157, 158] investigated acromegalic subjects, and interestingly, these two reports found contradictory results of increased [157] or reduced [158] levels of circulating EPCs compared to control subjects. Reasons for the discrepancy are unclear, however an interesting notion from these studies is that there seems to be an inverted U-shaped relationship between GH/IGF-1 and circulating EPC levels (i.e. these seems to be an optimal range of GH/IGF-1 for maintaining circulating EPC levels). Future investigations to explore mechanisms whereby IGF-1 can positively/negatively regulate EPC availability in vivo would be necessary to comprehend IGF-1's effects on endothelial repair.

There is evidence suggesting potential anti-oxidant effects of IGF-1 in vascular endothelial cells. IGF-1 promoted Nrf2-dependent antioxidant responses in cultured endothelial cells and low circulating IGF-1 levels impaired the Nrf2-dependent antioxidant response [159]. IGF-1 has been also shown to positively regulate expression levels of GPX1, a major anti-oxidant enzyme, and attenuate oxidative stress-induced premature senescence of endothelial cells [160]. Oxidative stress and premature senescence of endothelial cells is considered integral to the mechanisms of endothelial dysfunction, and thus causally related to atherosclerosis [161, 162]. Therefore, potential anti-oxidant effects of IGF-1 in the endothelium may contribute to the atheroprotective activity of IGF-1. Further studies are needed to investigate a direct link between the potential antioxidant effects of IGF-1 and reduction of atherosclerotic burden.

4. Modifiers and effectors of IGF-1 on the vasculature

Pregnancy-associated plasma protein A (PAPP-A) is a metalloproteinase and its known substrates are IGFBP-4, IGFBP-2, and IGFBP-5 [163, 164]. Circulating PAPP-A has been recognized for its positive association with prevalence of cardiovascular diseases [165–168]. There has been debate whether elevated PAPP-A levels are related to cardiovascular diseases [169, 170], and recent findings in animal models suggest a causal role of PAPP-A in vascular complications, such as injury-induced stenosis [171] and atherosclerosis [172–174], and also in metabolic dysfunction induced by high-fat/high-sucrose diet [175]. SMC-targeted overexpression of mutated PAPP-A, which is defective in IGFBP-4 proteolysis (Asp1499 to Ala) or both IGFBP-4 and −5 proteolysis (Glu483 to Ala), did not promote lesion formation, whilst an overexpression of wild-type (i.e. proteolysis-active) PAPP-A promoted lesion development, suggesting that proteolytic activity is essential for PAPP-A to promote atherosclerosis [176]. Since IGFBP-4 is considered inhibitory to IGF-1 action, proteolysis of IGFBP-4 should increase the bioavailability of IGF-1 to adjacent cells. In accordance with the notion, SMC-targeted overexpression of PAPP-A increased IGFBP-5 mRNA expression (known to be positively regulated by IGF-1) in aorta [173]. Therefore, it has been speculated that PAPP-A promotes atherosclerosis by liberating IGF-1 from IGFBP-4, thereby enhancing IGF-1 bioavailability [173, 176]. This is in contradiction to other reports showing atheroprotective effects of IGF-1 [45, 93, 95–98, 105]. PAPP-A's IGF-independent mechanisms of action remain a possibility. Of note, IGFBP-4 is known to have potent IGF-independent anti-angiogenic and anti-tumorigenic effects [177] and these effects are associated with anti-cathepsin B activity [178]. Pharmacological and gene therapy approaches have been attempted to test PAPP-A as a therapeutic target in animal models of atherosclerosis. Targeting of PAPP-A with a monoclonal antibody resulted in a 70% reduction in atherosclerotic burden in Apoe-null mice [179]. Stanniocalcin-2 is a protein that binds and inhibits PAPP-A, and AAV8-mediated overexpression of stanniocalcin-2 in liver reduced atherosclerosis in Apoe-null mice [180]. There reports suggest that systemic inhibition of PAPP-A may be a promising approach for treating atherosclerosis.

Diabetic status is a significant risk factor for atherosclerosis, and it has been shown that in vascular smooth muscle cells hyperglycemia diverts the IGF-1 signaling pathway from its canonical IRS-1-dependent phosphorylation cascades to a SHPS-1 mediated pathway,

leading to enhanced proliferation, migration, and dedifferentiation [181, 182]. Detailed mechanisms have been described indicating that the shift of IGF-1/IGF-1R signaling pathway is mediated via SHPS-1, which requires ligation of integrin αVβ3 with its ligand such as thrombospondin, vitronectin and osteopontin [183]. SMC expression levels of these ligands are elevated under hyperglycemic condition, consistent with hyperglycemia induced shift of IGF-1 signaling. In fact, a monoclonal antibody against αVβ3 integrin inhibited development of atherosclerotic lesions in diabetic pigs [184]. It has been also shown that hyperglycemia downregulates IRS-1, which should also contribute to the shift to the SHPS-1-dependent signaling pathway [182]. Moreover, hyperglycemia enhances smooth muscle cells' sensitivity to IGF-1 via p62/PKCζ-dependent NADPH-oxidase 4 upregulation [185], further promoting smooth muscle cell proliferation/migration. In light of the strikingly diverse phenotypes of SMC-derived cells within atherosclerotic plaques, it would be valuable to investigate potential consequences of the diversion of IGF-1R signaling pathways on phenotypic switching and pathologic intimal thickening.

Several miRNAs have been reported to regulate the IGF-1 system in cardiac tissue [186–189] or in arteries [190, 191]. miR-133a increased IGF1R mRNA half-life and IGF1R expression levels in SMCs, thereby promoting proliferation [190]. miR-490–3p is expressed in aortic SMCs and negatively regulates PAPP-A [191]. Of note, miR-490–3p was found to be downregulated in atherosclerotic plaques with a concomitant increase in PAPP-A levels [191], potentially enhancing IGF's effects.

Extracellular vesicles (EVs) are cell-derived spherical structures of various origins, including exosomes and microvesicles [192], which can transport proteins, mRNAs or non-coding RNAs. It has been suggested that EVs can positively regulate the IGF-1 system, leading to beneficial outcomes, such as enhancing angiogenesis in ischemic skeletal muscle [193] and protecting myocardium from ischemic damage[194, 195]. However, EVs could also negatively regulate the IGF-1 system, thereby inhibiting angiogenesis in diabetic heart [196] or potentially promoting apoptosis of endothelial cells [197]. IGF-1 may also regulate release of EVs. For instance, IGF-1 has been reported to facilitate release of EVs by cardiomyocytes and exert cardioprotection [198]. The potential role of EVs in modulating the IGF-1 system in atherosclerosis is largely unexplored.

5. Future perspectives

There is now a solid body of evidence testing IGF-1's effects in a cell-type specific manner using murine models of atherosclerosis. Thus far, outcomes of these investigations point to atheroprotective effects of IGF-1, and in particular the ability of IGF-1 to promote features of a more stable atherosclerotic plaque. Consistent with our observations, several clinical trials established a strong association between low IGF-1 (or high IGFBP levels) and increased risk of CVD. Yet, it should be noted that murine models of atherosclerosis have notable limitations [199], and outcomes in murine models cannot be directly inferred to the pathology of human disease. For instance rodents and humans have significant differences in mechanisms of lipid metabolism and in their immune systems, which play essential roles in the pathology of atherosclerosis [199]. Atherosclerotic plaques in mice rarely develop into atherothrombotic plaques [199], whereas in humans plaque erosion or rupture commonly

lead to acute ischemic events. Moreover, rodents do not seem to develop diffuse/adoptive intimal thickening, however large mammals such as pigs and horses are similar to humans [200–202]. Although there are no conventional animal models that develop spontaneous atherothrombotic events in a manner similar to human pathology, use of large animal models such as swine may in the future prove to be very informative [2, 199].

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Highlights

- Low circulating IGF-1 levels have been associated with cardiovascular diseases.
- Cell-type specific alterations of the IGF-1 system in animal models are consistent with atheroprotective effects of IGF-1.
- Evidence suggests beneficial roles of IGF-1 in the pathology of atherosclerosis.

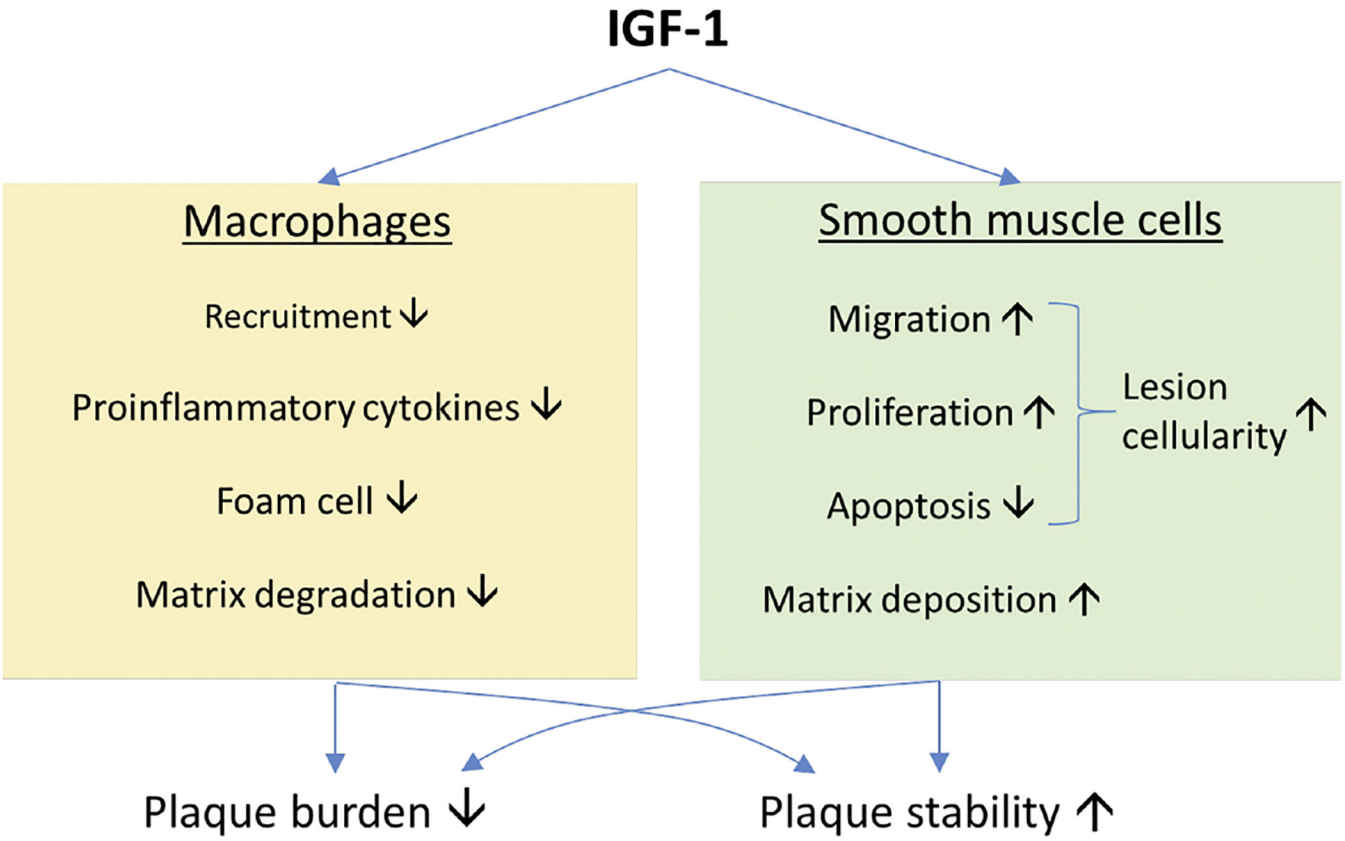

Figure. Cell-specific mechanisms underlying atheroprotective effect of IGF-1.

Cumulative reports of in vitro and in vivo investigations suggest that IGF-1 is suppressive to the recruitment of monocytes/macrophages to atherosclerotic plaques, production of proinflammatory cytokines, conversion of macrophages into lipid-laden foam cells, and extracellular matrix degradation. On the other hand, IGF-1 promotes smooth muscle cell (SMC) migration, proliferation and SMC-dependent matrix deposition. These cell-specific mechanisms may contribute to IGF-1-induced reduction in plaque burden and increase in plaque stability.