Obesity is a major risk factor for a number of cardiovascular diseases, and causes cardiac and vascular disease through well-known mediators including arterial hypertension, hyperlipidemia, and type-2 diabetes. Obesity is characterized by an excess of adipose tissue, which efficiently stores energy for times of starvation. In addition, multiple reports in the last decade have underlined the importance of white adipose tissue (WAT) as an endocrine organ. Several peptide hormones commonly referred to as adipokines are secreted by WAT, including leptin, adipin, acylation-stimulating protein (ASP), angiotensinogen, plasminogen activator inhibitor-1 (PAI-1), adiponectin, resistin, various cytokines including GM-CSF and G-CSF, and steroid hormones. Consequently, WAT peptide hormones and cytokines are involved in energy homeostasis, glucose and lipid metabolism, immune response, reproduction, and vascular homeostasis.

The exact molecular mechanisms of increased adipogenesis and its relation to the development of atherosclerotic lesions still remain unclear. One focus of research has been leptin, which was discovered in 1994 and is considered one of the important peripheral signals affecting food intake and body weight balance. Leptin reduces appetite and can reduce obesity in leptin deficient (ob/ob) knock-out mice. However, the initial enthusiasm over the discovery of leptin and its potential as fat-fighter for the obese has been absorbed by the facts, which reveal that in obese humans leptin levels are increased and mutations of the leptin receptor gene are rare events. There is a strong correlation of plasma leptin concentrations and atherosclerotic lesions, suggesting an important impact of leptin on plasma cholesterol concentrations and atherosclerotic lesion formation and progression. In this context, atherogenesis is accompanied by inflammatory and T-cell mediated responses. The accumulation of lipids in the subendothelial space leads to migration and proliferation of vascular smooth muscle cells and formation of the atherosclerotic plaque. Plaque progression and destabilization has also been associated with neovascularization.

Multiple lines of evidence envision an important role of leptin in atherosclerotic lesion formation and progression. In human umbilical vein endothelial cells and bovine aortic endothelial cells leptin increases the generation and accumulation of reactive oxygen species and enhances expression of monocyte chemoattractant protein-1. Leptin stimulates the production of proinflammatory cytokines from cultured monocytes and enhances the production of Th1 type cytokines from stimulated lymphocytes. LDL-receptor/leptin-deficient double mutant mice show extensively elevated lipid concentrations and atherosclerotic lesions, suggesting an important impact of leptin on plasma cholesterol metabolism.

Adipose tissue has enormous growth potential due to its energy storage function. Neovascularization is a critical step in adipose tissue growth and inhibition of angiogenesis is associated with adipose tissue loss and weight reduction. Treatment with leptin is known to enhance formation of capillary-like tubes and neovascularization in vitro and in vivo. Immunohistochemical analysis of human atherosclerotic plaques shows an increased expression of the leptin receptor in the neovascularized neointima.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Schäfer et al. introduce another interesting aspect to...
the numerous effects of leptin on the vascular wall. According to this study, wild-type mice with hyperleptinemia caused by a high fat diet showed a significantly enhanced neointimal and medial thickening of the vascular wall after induction of carotid artery injury with ferric chloride. In contrast, leptin-deficient (ob/ob) mice on a high fat diet did not show increased lesion formation despite an increase in body weight, glucose, and lipid levels. Daily leptin treatment of (ob/ob) mice resulted in a significantly increased lesion formation independent of the concomitant diet, whereas treatment of leptin receptor-deficient (db/db) mice with leptin did not alter vascular lesion progression, suggesting a direct, receptor-mediated effect of leptin on the vascular wall. Cell culture experiments and analysis of vascular smooth muscle cells within the neointima suggest a growth-stimulating effect of leptin on vascular smooth muscle cells. In concert with these findings, Stephenson et al. demonstrated that neointima formation after vascular injury was reduced in leptin receptor mutant mice. Evidence of an important role of leptin in restenosis in a clinical setting comes from the recently published results from Piatti et al., who investigated restenosis in 120 patients with insulin resistance and concomitant coronary heart disease undergoing coronary stenting. In in-stent restenosis, increased leptin and insulin levels were associated with a higher incidence of in-stent restenosis.

Leptin causes production of GM-CSF and G-CSF in murine macrophages and induces proliferation, differentiation, and functional activation of hematopoietic cells. The production of cytokines with effect on hematopoiesis might explain the presence of adipocytes within the bone marrow cavity. There is growing evidence that, in addition to the local proliferation of vascular smooth muscle cells (VSMCs), circulating, bone marrow-derived VSMC progenitors contribute to the neointima formation after severe vascular injury. Results from apolipoprotein E-deficient mice show a stromal-derived factor-1 (SDF-1) dependent mobilization and homing of VSMC progenitors to the vascular lesion site. Leptin is known to induce several cytokines and chemokines, and one may speculate that leptin may induce expression of SDF-1 on VSMC, governing the homing of VSMC progenitors to the lesion site. It is apparent there is a complex interaction between adipocytes and vascular cells involved in angiogenesis and neovascularization.

Leptin-receptors are not exclusively expressed on VSMCs, but are also expressed on endothelial cells and macrophages, suggesting an accessorial role in leptin-induced neointima formation. It is intriguing to speculate that, in addition to the multiple proatherogenic actions of leptin on the vascular wall, leptin may also influence vascular regeneration. Leptin-receptors are expressed on cultured endothelial cells, and stimulation of endothelial cells with leptin results in an increased proliferation and survival. Recent evidence underlines the important influence of adipose tissue on angiogenesis. Preadipocytes induce angiogenesis and vessel remodeling when implanted in vivo via a VEGF/VEGFR-2 dependent pathway. Interestingly, activation of VEGF-Receptor 2 induces the paracrine production of endothelial-cell-derived factors that promote adipocyte differentiation. Adipogenesis and angiogenesis are reciprocally regulated, and blockade of the important VEGF-signaling pathway results in an inhibition of adipose tissue formation. In a recently published study, Murad et al. localized leptin in wounds throughout the healing process after experimental wound induction. Leptin expression was rapidly induced in the inflammatory and proliferative phase of tissue repair. Neutralizing antibodies against leptin impaired healing progression. Interestingly, wound-derived leptin significantly increased systemic plasma levels 12 hours after induction of injury. These findings are in accordance with the above mentioned observations which underline the importance of leptin as a proangiogenic hormone involved in neovascularization. The mobilization of leptin may be regulated by hypoxemia since leptin gene expression is accelerated in ischemic tissues.

The presented results from Schäffer et al. put the still underdetermined role of leptin in atherosclerotic lesion progression in perspective. The described multiple effects of leptin on the vascular wall allow us to get a more detailed insight in the pathophysiology of obesity-associated atherogenesis. However, from epidemiological studies, we know that obesity is only a predisposing risk factor for coronary heart disease, which is known to worsen independent risk factors. It is conceivable that hyperleptinemia per se does not have detrimental effects on the vascular wall until the development of concomitant obesity-associated pathologies, such as the metabolic syndrome and insulin resistance. The effects of leptin on complex processes like atherosclerosis will thus not be confined to VSMCs, but will also affect endothelial cells and circulating peripheral blood cells. Surprisingly, the effects of leptin on endothelial cells (e.g., enhanced proliferation, increased survival) and angiogenesis suggest potentially beneficial effects of leptin on the vascular wall. Furthermore, leptin has been shown to increase local nitric oxide synthesis in a dose-dependent manner in normotensive rats and inhibit the release of neuropeptide Y (NPY), attenuating the vasoconstrictor effects of NPY.

Hence, there is much more to learn about the relation between leptin and vascular disease, which is also assumed to

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Interaction between adipocytes and the vascular wall. White adipose tissue-derived adipokines and leptin influence endothelial cells, VSMCs, and peripheral blood cells involved in atherosclerotic lesion formation and angiogenesis.
be independent of obesity. So far, leptin refuses to be pressed in a simple scheme as either a pro- or anti-atherogenic player. Clarification of the effects of leptin on vascular cells on the molecular level as well as prospective clinical investigations will help to condemn leptin as delinquent or redeemer.

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