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Review

Obesity and Atherosclerosis: Mechanistic Insights

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ABSTRACT

Obesity is a multifactorial chronic disease characterized by an accumulation of visceral and subcutaneous fat, which leads to a predisposition toward cardiometabolic diseases. A plethora of mechanisms, including abnormalities in lipid metabolism, insulin resistance, inflammation, endothelial dysfunction, adipokine imbalance, and inflammasome activation have been suggested to underlie the relationship between obesity and atherosclerosis. More recent data point toward an emerging role of impaired autophagy and altered gut microbiome homeostasis as potentially contributing factors. This review provides an overview of this area.

RÉSUMÉ

L'obésité est une maladie chronique multifactorielle caractérisée par une accumulation de graisse viscérale et de graisse sous-cutanée, qui entraîne une prédisposition aux maladies cardiométaboliques. Une pléthore de mécanismes, dont les anomalies du mécanisme des lipides, l'insulinorésistance, l'inflammation, la dysfonction endothélial, le déséquilibre des adipocytokines et l'activation de l'inflammasome ont été suggérés pour étayer le lien entre l'obésité et l'athérosclérose. Des données plus récentes suggéraient comme rôle émergent à la déficience de l'autophagie et à l'altération de l'homéostasie du microbiome intestinal d'être des facteurs potentiellement contributifs. La présente revue donne un aperçu de ce domaine de recherche.

Obesity is a major risk factor for atherosclerotic vascular disease and cardiometabolic syndrome. Various mechanisms have been suggested to link obesity to atherosclerosis. These are detailed in Table 1 and are reviewed herein.

Adipokine Imbalance

The visceral adipose tissue is a source of numerous adipokines, most of which are deemed to be proinflammatory. Increasing evidence suggests that an imbalance between proinflammatory vs anti-inflammatory adipokines (such as adiponectin) might be responsible for the development of insulin resistance and endothelial dysfunction and atherosclerosis in patients with obesity (Fig. 1).

Adiponectin is the most abundant anti-inflammatory and vasculoprotective adipokine secreted by adipose tissues. Numerous studies have to date demonstrated that plasma levels of adiponectin are lower in patients with obesity and/or diabetes. Adiponectin improves insulin sensitivity by increasing energy expenditure and fatty acid oxidation through the phosphorylation of 5-adenosine-monophosphate-activated protein kinase, and via an increase in the expression of peroxisome proliferator-activated receptor-α target genes such as CD36, acyl-coenzyme oxidase, and uncoupling protein 2.[2] The adiponectin receptors, AdipoR1 and AdipoR2, are responsible for mediating the metabolic actions of adiponectin.

Adiponectin exerts its vasculoprotective effects through a multitude of pathways. In vitro, adiponectin induces nitric oxide (NO) production in human aortic endothelial cells via activation of the 5-adenosine-monophosphate-activated protein kinase pathway and enhancement of endothelial NO synthase (eNOS) activity.[3] Adiponectin additionally suppresses proliferation and superoxide generation, and also enhances eNOS activity in endothelial cells treated with oxidized low-density lipoprotein.[4] Adiponectin has also been demonstrated to attenuate the adhesion of monocytes to endothelial cells, primarily via a mechanism that involves inhibition of tumour necrosis factor (TNF)-α- and interleukin (IL)-8-induced synthesis of intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), and E-selectin.[5] Adiponectin suppresses the expression of class A macrophage scavenger receptors and consequently reduces foam cell formation and decreases secretion of proinflammatory cytokines.[6] Notably, foam cell formation is further reduced by adiponectin-induced downregulation of acyl-coenzyme A:cholesterol acyltransferase-1 in macrophages, the enzyme that catalyzes the formation of cholesteryl esters.[7] Accordingly, adiponectin limits the initiation of atherosclerotic plaque formation. Recent data point toward the ability of adiponectin to prime monocyte differentiation toward the anti-inflammatory M2 macrophage lineage,[8] and

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Table 1. Suggested mechanisms of obesity-induced atherosclerosis

Endothelial dysfunction
Adipokine imbalance
Vascular inflammation
Macrophage NLRP3 inflammasome activation
Altered gut microbiome
Loss of autophagic flux
Oxidative stress

that in states of adiponectin deficiency (such as obesity), monocytes might be primarily driven toward the proatherosclerotic M1 lineage. Physiological concentrations of adiponectin significantly suppress the proliferation and migration of human aortic smooth muscle cells induced by platelet-derived growth factor BB in vitro[9] by directly binding platelet-derived growth factor-BB and inhibiting growth factor-stimulated extracellular signal-regulated kinase signalling. These results suggest that adiponectin might also prevent vascular remodelling in atherosclerosis. In other studies, adiponectin has been shown to selectively increase the expression of tissue inhibitor of metalloproteinase-1 in human monocyte-derived macrophages,[10] suggesting that it might favour plaque stabilization. Via improving vascular function, adiponectin has been recently implicated in protection against sepsis induced multiorgan dysfunction.[11] In vivo studies in mice have confirmed the antiatherogenic properties of adiponectin. Adiponectin-deficient mice, compared with wild type controls, show neointimal thickening and increased proliferation of vascular smooth muscle cells after mechanical injury to arteries.[12] Adenovirus-mediated delivery of adiponectin in these mice considerably attenuated the extent of neointimal proliferation.[12] Furthermore, treatment of apolipoprotein E-deficient mice ($ApoE^{-/-}$) with adiponectin-expressing adenoviruses reduced atherosclerotic lesion formation compared with control mice.[13] Taken together, the balance of published information would strongly associate low adiponectin levels in obesity as a causal and/or permissive basis of atherosclerotic risk.

Resistin is a proinflammatory adipokine that is released in excess amounts in individuals with visceral adiposity. Resistin profoundly upregulates the expression of TNF-α and IL-6 in human peripheral blood mononuclear cells.[14] Human resistin has been reported to stimulate the synthesis of proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-12 in various cell types through a nuclear factor-κB-dependent pathway.[15] A positive correlation between resistin levels and vascular inflammation has been demonstrated in obese humans.[16] As further evidence of its proinflammatory profile, resistin upregulates the expression of adhesion molecules VCAM1 and ICAM1, and induces chemokine (C-C motif) ligand 2 and endothelin (ET)-1 release in human endothelial cells.[17] Indeed, we demonstrated that resistin directly triggered endothelial cell activation by promoting ET-1 release, in part by inducing ET-1 promoter activity via the activator protein-1 site. Furthermore, resistin upregulated the expression of adhesion molecules and chemokines and downregulated tumor necrosis factor receptor-associated factor-3, an inhibitor of CD40 ligand signalling in endothelial cells. Therefore, increased resistin levels might be another factor that contributes to obesity-induced atherosclerosis.[17]

The adipokine, leptin, has a main function to control food intake and energy expenditure.[18] Levels of circulating leptin fluctuate; they are increased with overfeeding and decreased with starvation. Mice with a mutation in the gene encoding leptin (ob/ob mice) or the gene encoding the leptin receptor (db/db mice) have obese phenotypes,[19] and also exhibit increased atherosclerosis.[20] Leptin is considered to be a proinflammatory cytokine and is structurally similar to other proinflammatory cytokines such as IL-6, IL-12, and the

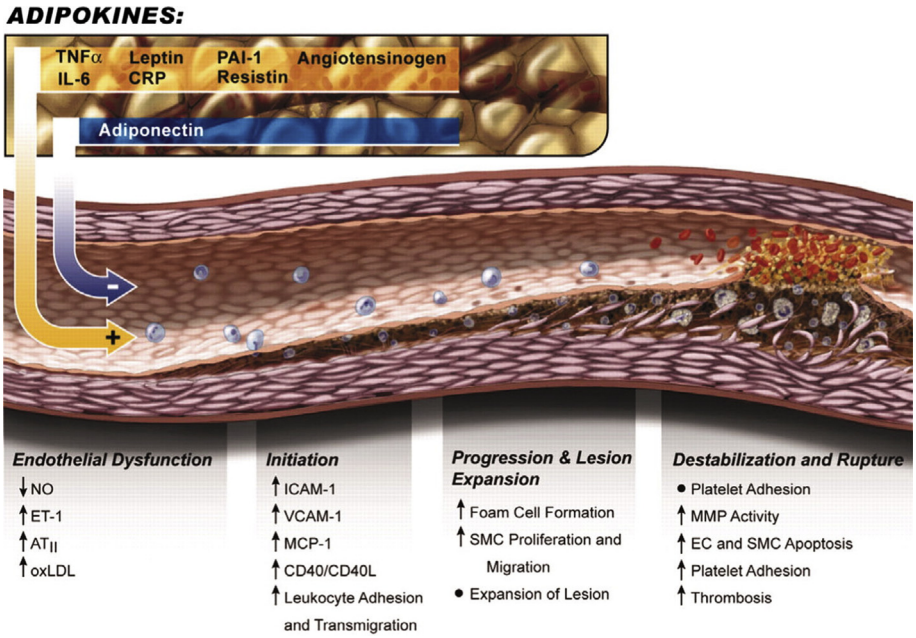

Figure 1. Anti- and proinflammatory adipokines. AT, angiotensin II; CRP, C-reactive protein; EC, endothelial cell; ET-1, endothelin-1; ICAM, intercellular adhesion molecule; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; NO, nitric oxide; oxLDL, oxidized low-density lipoproteins; PAI-1, plasminogen activator inhibitor-1; SMC, smooth muscle cell; TNF, tumour necrosis factor; VCAM, vascular cell adhesion molecule. Reproduced from Lau et al.[1] with permission from American Physiological Society. Copyright © 2014, The American Physiological Society.