Editorial Comment

Low Adiponectin Level Causes Vascular Remodeling?: A Perspective through Intravascular Ultrasound

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Vascular Remodeling Evaluated by Intravascular Ultrasound

Intravascular ultrasound (IVUS) allows direct visualization of the coronary arterial wall and plaque, and the safety of this approach has been confirmed. Serial changes in the size and character of coronary atheromatous plaques can be evaluated by serial IVUS follow-up studies. IVUS has thus become the reference method for quantification of plaque volume and evaluation of plaque growth in trials of therapeutic interventions (*1*). In a recent simultaneous comparison study of IVUS and quantitative coronary arteriography (QCA) (*2*), a good correlation was identified between measures of lumen size by IVUS and QCA, but plaque volume and changes on IVUS were totally unrelated to minimum lumen diameter or percent stenosis and changes on QCA. One explanation for the lack of correlation between IVUS and QCA may be "vascular remodeling." Despite plaque growth, lumen area can be preserved by outward vascular remodeling (positive remodeling) (*3*). Positive coronary artery remodeling is considered as a process of atherosclerosis and is often associated with plaque rupture in acute coronary syndrome (*4*) and a higher risk for no-reflow phenomenon after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (*5*).

Vascular Remodeling and Adiponectin

Adiponectin is the most abundant adipose-specific protein secreted from adipose tissues and low adiponectin levels contribute to the development of obesity-linked illness. The report by Iwata *et al*. (*6*) in the previous issue of *Hypertension Research* represents the first reported of an association between parameters of IVUS and metabolic factors in patients with stable coronary arterial disease who underwent PCI. The major findings are that: 1) independent predictors of plaque volume include hemoglobin A1c (standardized regression coefficient, 0.26; $p<0.03$) and diastolic blood pressure (standardized regression coefficient, 0.39; $p<0.02$), as well as high low-density lipoprotein-cholesterol (LDL-C) level (standardized regression coefficient, 0.31; $p<0.009$); and that 2) plasma adiponectin level represents an independent risk factor for positive vascular remodeling (odds ratio, 0.81; 95% confidence interval, 0.69–0.96; $p<0.006$). Consequently, plasma adiponectin levels in patients with positive remodeling were significantly lower than those in patients with non-positive remodeling, although the underlying mechanisms remained unclear.

These cross-sectional study results are in line with previous *in vitro* and *in vivo* experimental data. From *in vitro* studies, adiponectin has been reported to suppress the proliferation of smooth muscle cells (SMCs) and inhibit their migration *via* inhibition of various growth factors and extracellular signal–regulated kinase (ERK) signaling in SMCs (Fig. 1) (*7*, *8*). From *in vivo* studies, acute vascular injury leads to increased neointimal hyperplasia and proliferation of SMCs in adiponectin knock-out mice compared with those in wild-type mice. This unfavorable phenomenon in adiponectin knock-out mice was reversed by adenovirus-mediated adiponectin expression (*9*). Adiponectin also stimulates nitric oxide (NO) production in vascular endothelial cells partly *via* the adenosine monophosphate (AMP) activated protein kinase (AMPK) signaling pathway (*10*) and suppresses the attach-

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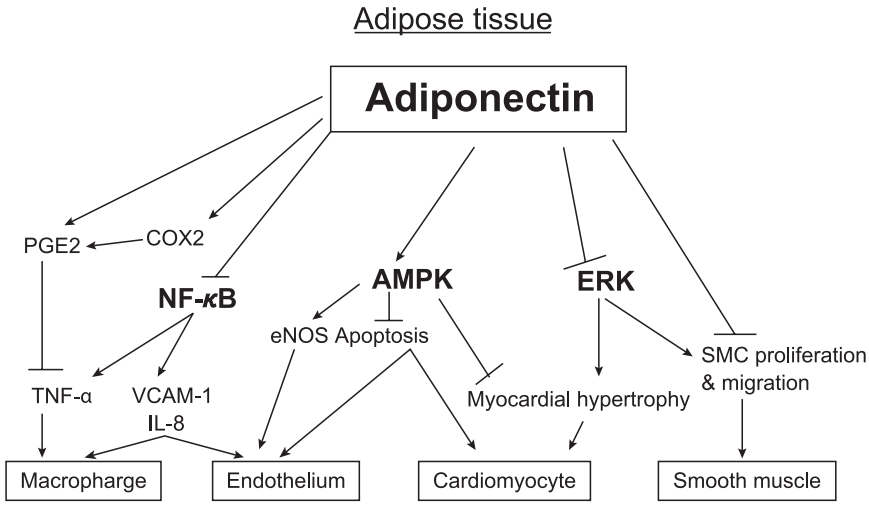

Fig. 1. *Adiponectin suppresses activation of nuclear factor (NF)-κB, which is a key player of inflammation. Adiponectin also suppresses extracellular signal–regulated kinase (ERK), which enhances smooth muscle cell (SMC) proliferation and cardiac hypertrophy. In contrast, adiponectin activates the 5′-adenosine monophosphate activated protein kinase (AMPK) signaling cascade, which displays multiple functions such as enhancement of endothelial nitric oxide synthase (eNOS) and inhibition of apoptosis. COX2, cyclooxygenase 2; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; IL-8, interleukin-8.*

ment of monocytes to endothelial cells through the nuclear factor κB pathway (*11*). Collectively, these data suggest that adiponectin may improve endothelial function, prevent the proliferation of SMCs at vascular lesions, and finally suppress vascular remodeling as shown by Iwata *et al*. (*6*).

Adiponectin and Cardiovascular Disease

The role of adiponectin in cardiovascular disease remains controversial (*12*), although experimental and clinical evidence has been accumulated regarding anti-inflammatory (*10*, *11*), anti-atherosclerotic (*6–9*) and anti-diabetic effects (*13*). Recent prospective large-scale studies (*14–16*) have reported that plasma adiponectin level does not correlate with incidence of coronary arterial disease. High adiponectin levels have been observed as a predictor of poor prognosis in several selected populations with heart failure (*17–19*), renal dysfunction (*20*) and aged groups (*19*). In those selected populations, accumulation of adiponectin in patients with heart failure or chronic kidney disease may reflect the malnutrition that characterizes these disease states and is thus a marker of poor prognosis (*20*). Further investigations from multiple aspects including IVUS are warranted to clarify the role of adiponectin in risk of cardiovascular disease.

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