Editorial

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Chemerin: A Novel Link between Inflammation and Atherosclerosis?

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Many factors contribute to the development of atherosclerosis. Over the past few years, understanding of the importance of inflammation during all stages of atherosclerosis, including its initiation through the progression and the complication of thrombosis, has increased greatly. Under normal conditions, the vessel wall has its own machinery to maintain vascular homeostasis. However, the balance is broken when repetitive metabolic stimuli resulting from hypertension, insulin resistance or obesity strike the vessel wall. Most of these metabolic stimuli disturb homeostasis through the initiation of inflammation, that is the recruitment of inflammatory cells, the increased adhesion molecules, secretion of chemoattractant and proinflammatory cytokines from the endothelial cells and the migration and proliferation of smooth muscle cells from media [1]. Among the top contributors of inflammatory stimuli are adipokines secreted from adipose tissue, which is now considered not as a mere mass of fat tissue, but an active organ that acts as a reservoir for energy in the energy excess state and as an active supplier of energy when the body runs short of it. Adipokines have diverse autocrine, paracrine and endocrine actions and have been implicated in the pathogenesis of metabolic syndrome and cardiovascular disease.

Chemerin, also known as tazarotene-induced gene 2 protein (TIG2) or retinoid acid receptor responder 2 (RARRES2), was a recently identified novel adipokine that has a role in adaptive and innate immunity [2]. Chemerin acts as a secreted ligand of the orphan G protein-coupled receptor chemokine-like receptor (CMKLR) 1, chemokine (C-C motif) receptor-like (CCRL) 2 and the G protein-coupled receptor (GPR) 1. Various cell types involved in innate and adaptive immunity express CMKLR1, and chemerin is known to function as a chemoattractant that promotes recruitment of immune cells to sites of injury [3,4]. Chemerin is translated as a pre-protein that is secreted as a proprotein following the proteolytic cleavage of a signal peptide [3,5]. This proprotein has low biological activity, and requires further C-terminal processing by plasmin, carboxypeptidases or serine protease of the coagulation, fibrinolytic and inflammatory cascades. This processing is suggested to be the key regulatory mechanism that affects the concentration of bioactive chemerin.

Increased chemerin expression in adipocytes was demonstrated in mice fed a high fat diet [6]. Chemerin is known to be induced during adipocyte differentiation and increases insulin-stimulated glucose uptake in adipocytes [7]. A recent study suggested that overexpression of human chemerin in low-density lipoprotein receptor knockout (LDLRKO) mice induced insulin resistance in skeletal muscle and administration of chemerin exacerbated glucose intolerance, lowered insulin levels, and decreased tissue glucose uptake in obese/diabetic mice [8]. In addition, chemerin is shown to be expressed differentially according to different fat depots [9]. In human studies, chemerin levels correlated with metabolic factors re-

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lated to obesity, such as body mass index, triglyceride levels and blood pressure [10]. It has been reported that CMKLR1 is expressed in vascular endothelial cells and that its expression level is regulated by inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, or IL-6 [11]. A very recent study also shows the role for chemerin/CMKLR1 signaling in clonal expansion during adipocyte differentiation in bone marrow mesenchymal stem cells through the interaction with peroxisome proliferator-activated receptor gamma (PPARγ), a master regulator of adipocyte differentiation [12]. These data show that chemerin is correlated with adipocyte differentiation, glucose metabolism, and inflammation, suggesting its role in the pathophysiology of obesity, metabolic syndrome, and possibly type 2 diabetes mellitus.

Although accumulating data suggest a plausible role of chemerin in metabolic disorders, its role in atherosclerosis still remains elusive. Serum chemerin levels were reported to be weakly correlated with coronary plaque burden and the number of non-calcified plaques in humans, although the significance disappeared after adjustment for the cardiovascular disease risk factors [9]. Another study demonstrated that aortic and coronary atherosclerosis assessed in 41 autopsy cases was positively correlated with chemerin expression in periaortic and pericoronary adipose tissue, suggesting the paracrine effects of chemerin on atherosclerosis [13]. Overexpression of chemerin in LDLRKO mice did not affect the atherosclerotic lesion area determined by *en face* analysis of the entire aorta [8]. The plausible mechanisms of the relationship between chemerin and development of atherosclerosis could be as follows: 1) the accumulation of chemerin in an atherosclerotic lesion could attract immune cells which contribute to the remodeling of the vessel wall, 2) the alteration of insulin sensitivity and glucose uptake in adipocytes and skeletal muscle could contribute to development of atherosclerosis, and 3) chemerin could directly affect the inflammatory status in vascular endothelial cells by increasing the production of nitric oxide via the activation of PI3K/Akt/eNOS pathways (Fig. 1) [14].

In this issue, Hah et al. [15] reported that subjects with multiple stenotic coronary vessels showed higher serum chemerin levels than the subjects with only one stenotic coronary artery. However, when logistic regression analysis was performed with

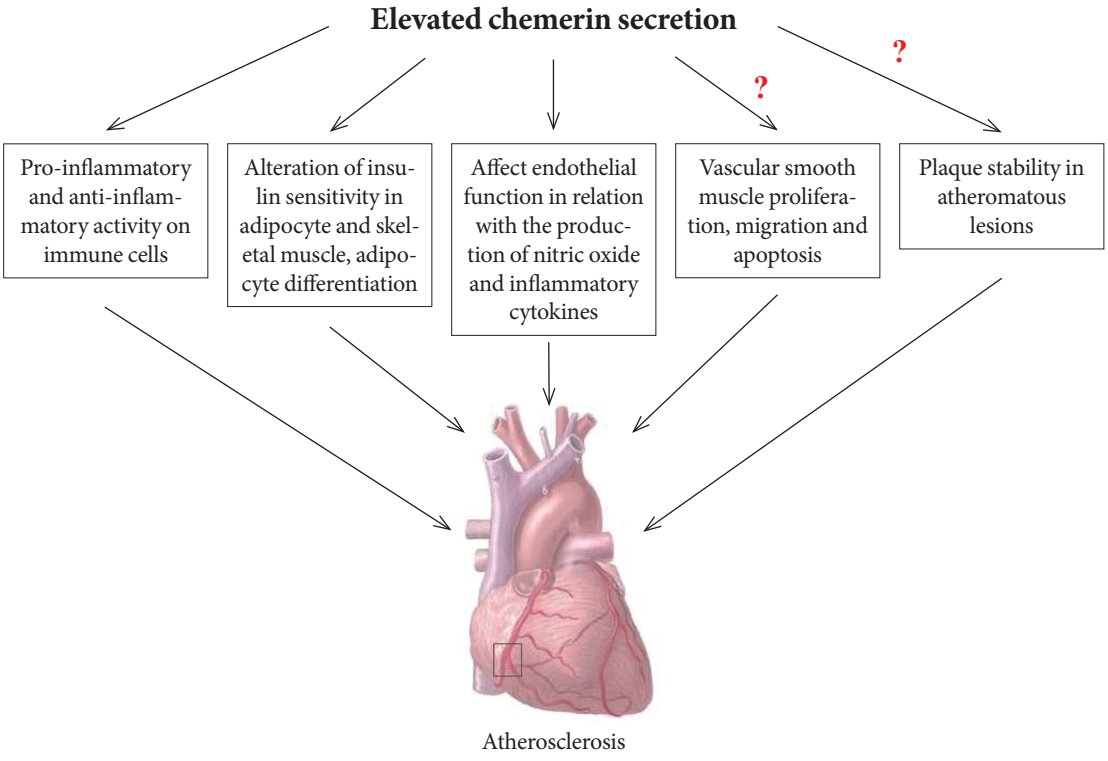

Fig. 1. The proposed mechanism of the role of chemerin in atherosclerosis.

conventional cardiovascular risk factors, such as C-reactive protein and low density lipoprotein cholesterol, chemerin was not an independent risk factor of multiple vessel disease. This study has implication in that it was the first study to assess atherosclerosis directly by coronary angiogram, although the absolute number of subjects was small. The disappearance of significance of chemerin as the determinant of coronary artery stenosis after adjustment for cardiovascular risk factors suggests that the influence of chemerin on the development of atherosclerosis might be explained more by the metabolic factors and the factors related with adipose tissues than the direct effects of chemerin on the initiation and progression of atherosclerotic plaque formation. However, there are other aspects involved in the development of atherosclerosis not yet studied in relation with chemerin expression, such as the effects of chemerin on vascular smooth muscle cell proliferation and migration, apoptosis, or plaque stability (Fig. 1). More study is needed to elucidate the role of chemerin in atherosclerosis and cardiovascular diseases.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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