Telomere Shortening, Atherosclerosis, and Metabolic Syndrome

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Atherosclerotic lesions are characterized as accumulations of cholesterol esters and pathologic reactions by various cell groups. The pathogenesis of atherosclerosis has been discussed primarily on the basis of these two phenomena. A well-known concept to understand the etiology of atherosclerosis is the theory of response to injury. According to this theory, physiologically active substances such as platelet-derived growth factor (PDGF) are released in response to injury of the vascular wall, and these substances induce pathologic reactions such as migration and proliferation of vascular smooth muscle cells (1).

Atherosclerotic lesions are composed of various types of cells, including platelets, endothelial cells, macrophages, smooth muscle cells, and T lymphocytes. These cells release cell growth factors and cytokines to maintain the homeostasis of the vascular wall exposed to risk factors such as hypercholesterolemia, hypertension, diabetes mellitus, and smoking that promote the development of atherosclerosis. This mechanism resembles inflammatory reactions to exogenous factors and the wound healing process (2). Dysfunction of vascular endothelial cells is thought to induce a cascade of pathologic reactions of cell groups mediated by the expression of adhesion molecules, resulting in infiltration of mononuclear cells, foam cell formation, promotion of thrombus formation, and disturbed relaxation of blood vessels.

Eukaryotic chromosomes end with telomeres, which comprise tandem repeats of the sequence TTAGGG, and are involved in the stabilization of chromosomal ends. It is well known that telomeres progressively shorten with repeated cell division and aging. There is a negative correlation between age and telomere length of peripheral blood mononuclear cells. It has been suggested that the cellular dysfunction that accompanies senescence of vascular cells could contribute to the development of atherosclerosis. Recent studies have demonstrated that telomere shortening is related to various pathological conditions including atherosclerosis (3). Here, Obana et al demonstrated that telomere shortening could be involved in the development of atherosclerotic disease in patients with metabolic diseases such as hypercholesterolemia and diabetes mellitus (4).

Diabetes mellitus, hyperlipidemia, hypertension, and obesity, which serve as a basis for the development of atherosclerosis, are induced by a genetic predisposition coupled with environmental factors (5). Hypernutrition and insufficient exercise lead to diabetes mellitus, hyperlipidemia, hypertension, and obesity in individuals genetically predisposed to these disorders, which eventually produce ischemic heart disease and cerebrovascular disease.

The term "metabolic syndrome" has been proposed to indicate individuals with high risk in whom multiple risk factors precipitates ischemic cardiac disease, although each individual risk factor is not severe when taken into consideration separately. Reaven used the term "syndrome X" to indicate cases in whom hyperinsulinemia, IGT, low blood HDL (high-density lipoprotein)-cholesterol level, high blood VLDL (very low density lipoprotein) triglyceride level, and hypertension are all present, and he emphasized a significant role of insulin resistance in the clustering of risk factors (6). Visceral fat syndrome caused by accumulation of visceral fat has also been proposed (7).

These conditions are accompanied by certain concomitant metabolic factors such as obesity, hypernutrition, and insufficient exercise. It has been suggested that there are common molecular mechanisms causing metabolic syndrome in which expressions of genes related to glucose metabolism, lipid metabolism, and vascular function are regulated by various transcriptional factors such as PPARs and SREBPs. It is interesting to know the causal relationship between the molecular mechanisms underlying the metabolic syndrome and telomere shortening in vascular cells.

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References