Vascular risk factors

Aging

Adipose tissue

Liver

Artery

IL-6

CRP

Apathy

DWMLs

Adipose tissue

Liver

Aging

Artery

IL-6

CRP

Vascular risk factors

Monocyte activation/migration

T cell activation/migration

Endothelial dysfunction

Platelet aggregation

Necrotic core formation

Smooth muscle cells proliferation

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T cell activation/migration

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Smooth muscle cells proliferation
Supplementary Figure 1. Retention of low-density lipoprotein (LDL) particles in the vessel wall is the first step of atherosclerosis; when LDL particles are trapped in an artery, LDL undergoes oxidation. Oxidized LDL (Ox-LDL) induces pro-inflammatory responses via a lectin-like oxidized LDL receptor-1. Endothelial cells activated by Ox-LDL express leukocyte adhesion molecules such as intracellular adhesion molecule-1 and vascular cell adhesion molecule-1, which increase the adhesion and migration of monocytes into the arterial wall. After migration, the monocytes differentiate into macrophages and express scavenger receptors on the cell surfaces. The internalization of Ox-LDL by means of the scavenger receptors leads to the formation of lipids oxidation and the accumulation of cholesterol esters (i.e., the formation of foam cells and plaques). As plaques evolve, activated macrophages and T cell lymphocytes are involved in the advanced atherosclerotic lesion or plaque progression. Endothelial dysfunction is a primary step in atherosclerosis development as noted by increased endothelin-1 (ET-1) expression and decreased nitric oxide (NO) production. Ox-LDL also increase the expression of growth factors (e.g., platelet-derived growth factor and fibroblast growth factor) for the migration and proliferation of smooth muscle cells, leading to the thickening of plaques, formation of a necrotic core, and ultimately plaque rupture. Atherosclerosis of the cerebral arteries induces hypoperfusion in the watershed zone between the basal ganglia perforation arteries and medullary arteries, thereby causing deep white matter lesions (DWMLs). C-reactive protein (CRP) is produced by hepatocytes under the regulatory control of circulating IL-6 from atherosclerotic lesions and from adipose tissue.