The deleterious effects of high low-density lipoprotein (LDL) cholesterol levels on atherosclerosis has been known for almost a century, yet plasma cholesterol continues to be a challenge for clinicians in the treatment and prevention of cardiovascular disease. Atherogenesis involves uptake of cholesterol in the vascular wall, followed by inflammatory activation and growth of vascular smooth muscle cells. Indeed, proinflammatory mediators such as interleukins and cytokines stimulate vascular cell growth and atherogenesis (reviewed in), whereas inhibition of inflammatory pathways attenuates cell growth and atherosclerosis. Therefore, we now view atherosclerosis as a vascular inflammatory process as already proposed by Virchow and later by Anitschkow who noticed an “infiltrative character” of atherosclerotic lesions of cholesterol-fed animals.

Differentiation and growth of vascular smooth muscle cells, a prerequisite of atherosclerosis progression, depends on a fine-tuned balance between activators and inhibitors of cell growth. In the 1980s, Libby and colleagues reported that LDL cholesterol enhances growth factor–stimulated proliferation of vascular smooth muscle cells. Later, it became clear that the growth-stimulating effects of LDL cholesterol also involves oxidative stress–dependent activation of mitogen-activated protein kinases. Oxidative stress leads to the formation of so-called oxidized phospholipids, small molecules formed from fatty acids. This oxidation of phospholipids such as phosphatidylcholine, present in LDL and cell membranes, is mediated by reactive oxygen species and lipoxygenases at the sn-2 position of polyunsaturated fatty acid residues, resulting in the formation of either complete or truncated forms of oxidized phospholipids. Oxidation of phosphatidylcholine–containing lipids, namely of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (PAPC), results in several oxidized phospholipids including 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine (POVPC) and 1-palmitoyl-2-glutaroyl-sn-glycero-3-phosphocholine (PGPC), which are known proinflammatory molecules. Oxidized phospholipids, particularly POVPC, are present in lipoproteins from which they can directly translocate to the plasma membrane of vascular smooth muscle cells (Figure). Of note, selected oxidized phospholipids increase monocyte adhesion to endothelial cells and kinase activation, and angiogenesis, all of which are promoters of atherosclerosis. At high concentrations, oxidized phospholipids promote vascular smooth muscle apoptosis, which may influence plaque vulnerability of atherosclerotic lesions.

In the present issue of Circulation Research, Pidkova and coworkers present new and important evidence supporting a direct proatherogenic role of oxidized phospholipids. These investigators report that oxidized phospholipids, and specifically POVPC, at physiological concentrations, are crucial for cellular differentiation and growth of vascular smooth muscle cells in vivo and in vitro. Exposure to oxidized phospholipids inhibited cell differentiation at the level of differentiation marker genes (smooth muscle cell α-actin, myosin heavy chain), which these investigators found to be dependent on Krüppel-like transcription factor (KLF4), a known repressor of cellular differentiation. In contrast, myocardin, a serum response cofactor and inductor of genes important for a differentiated, nonproliferative vascular smooth muscle cell phenotype, was downregulated after exposure to oxidized phospholipids (Figure). At the same time, oxidized phospholipids increased expression of proinflammatory genes and stimulated growth and apoptosis in vascular smooth muscle cells. The stimulating effects on migration and proliferation in vascular smooth muscle cells were seen using similar concentrations of POVPC present in atherosclerotic vessels.

Why are these data important? First, they demonstrate novel mechanisms by which high levels of oxidized phospholipids accelerate vascular smooth muscle cell growth and apoptosis. Oxidative stress represents a common feature of all known cardiovascular risk factors and is a key mechanism leading to formation of oxidized phospholipids. Moreover, LDL cholesterol contains high concentration of oxidized phospholipids, reminding us that lowering of plasma cholesterol will consequently help to reduce oxidized phospholipids levels. Finally, the results presented by Pidkova et al provide yet another piece adding to the puzzle of how inflammatory pathways contribute to cell growth and atherogenesis. It appears reasonable to speculate that either lowering of LDL-bound concentrations or the generation of oxidized phospholipids will reduce clinical manifestations of atherosclerosis. Understanding and communicating the importance of inflammation and oxidative stress for the progression of atherosclerosis reminds us that control and treatment of risk factor such as high cholesterol remains an important goal to reduce atherosclerosis in adults and particularly in children.

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