New Strategies of LDL Lowering: From Bench to Clinical Work

Chu-Huang Chen, M.D., Ph.D.

Associate Professor
Clinical Director, Behavioral Medicine Research Center
Section of Atherosclerosis and Lipoprotein Research
Department of Medicine
Baylor College of Medicine
6565 Fannin, M.S. A-601
Houston, Texas 77030
U. S. A.
Tel: (1) 713-798-4217
E-mail: cchen@bcm.tmc.edu

ABSTRACT

Low-density lipoprotein (LDL) is generally known as "bad cholesterol", an infamous nickname it earns for causing vascular diseases. The truth is, LDL is only bad when there is too much LDL-cholesterol (LDL-C) circulating in the body. But, when exactly is LDL-C "too much"? The answer to this question keeps changing as our understanding of this particle advances. LDL is a heterogeneous group of lipoproteins and not all LDL particles are the same. By subjecting LDL to a process called fast protein liquid chromatography, we are able to divide it into 5 subfractions according to their electrical charge. L5 is the 5^{th} and last eluted group and is most electronegative among all subfractions. It is also mildly oxidized in nature. L5 is only present in patients with elevated plasma LDL-C concentrations, patients with diabetes, and people who smoke even though otherwise healthy. In healthy subjects who do not have elevated LDL-C, diabetes, or a smoking habit, L5 is not present. L5 is a biological nanoparticle with a diameter of 20-30 nm. When added to vascular endothelial cell cultures, L5 inhibits proliferation and induces apoptosis. Apoptosis of endothelial cells will increase endothelial permeability, leading to eventual atherosclerosis. At a later phase, it also contributes to clot formation on the surface of the atherosclerotic plaque, resulting in complete vascular occlusion. Tissue hypoxia and ischemia induce compensatory angiogenesis, a process that requires endothelial progenitor cells. In our studies, L5 inhibits normal differentiation of endothelial progenitor cells from monocytes. It also inhibits the formation of capillaries from mature endothelial cells. Thus, L5 not only induces endothelial cell apoptosis, but also inhibits angiogenesis. How is this accomplished? L5 exerts these adverse effects by first entering the cell through the LOX-1 receptor. By labeling the L5 nanoparticle with a dye called DiI, we can observe the internalization of DiI-L5 under the microscope. After entering the cell, L5 may have close contact with important cellular compartments, including the mitochondria, endoplasmic reticulum, and, eventually, the nucleus. L5 may or may enter these compartments, and they may or may not have been metabolized before they or their active components induce a cascade of biological reactions in these compartments. One of the primary mechanisms of L5 is disruption of intracellular signaling that involves an FGF2-PI3K-Akt autoregulatory loop. The integrity of the FGF2-PI3K-Akt loop is essential to cell survival. When this loop is dysfunctional, the cells cannot proliferate and will eventually die from apoptosis. At low concentrations, L5 does not cause apoptosis of the differentiating cells, but stop their differentiation so that endothelial progenitor cells will not be formed. Thus, L5 is a critical pathological entity and should be considered a new target of cholesterol treatment.