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·专题报告·

Development of Novel Therapeutics to Raise HDL and Block Inflammation

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Plant derived phospholipids are rich in linoleic acid (LA) and have therapeutic value to treat inflammatory diseases of the liver, intestine and vasculature. These phospholipids act to normalize plasma lipid levels and prevent atherosclerotic disease. Oral administration of LA-phospholipids to cholesterol-fed rabbits prevents the development of atherosclerosis. Human trials have shown that plant derived phospholipids are safe and can significantly increase plasma HDL-cholesterol levels by up to 20%. Studies in hepatocytes have shown that LA-phospholipids, such as dilinoleoyl phosphatidylcholine (DLPC), promote a 4-fold stimulation in HDL secretion, through an activation of PPARα. DLPC has no affect on cellular apoA I mRNA levels, but acts through membrane ATPase and G-protein pathways to block the reuptake and degradation of apoA I. Factors that increase HDL production impact inflammatory diseases by

directly affecting cellular inflammatory pathways. Pro-inflammatory agonists inhibit hepatic apoA I secretion. DLPC is able to block both a lipopolysaccharide (LPS) and tumor necrosis factor (TNFα) mediated inhibition of apoA I secretion. DLPC directly affects inflammation through an inhibition of nuclear factor-kappa B (NF-κB). DLPC is able to block TNFα activation of MAP kinase, by blocking ERK1/2 phosphorylation. DLPC blocks LPS and TNFα activation of NF-κB pathways by inhibiting IκBα and NF-κB phosphorylation. LA-phospholipids act as anti-inflammatory agents in hepatic, intestinal and neuronal cells by blocking NF-κB activation. A stimulation of hepatic HDL production appears to be partly an anti-inflammatory response and requires both an activation of PPARα and inhibition of NF-κB. Phase II testing is now required to evaluate the therapeutic value of LA-phospholipids to raise plasma HDL levels and prevent cardiovascular disease.

(Edited by LI Xiao-Ling)