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Oxidative Modification of Low Density Lipoproteins by Human Polymorphonuclear Leukocytes

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Summary: Oxidatively modified low density lipoproteins are thought to play an important role in the generation of macrophage-derived foam cells in early atherosclerotic lesions. Cultured endothelial cells, monocytes, macrophages and smooth muscle cells can modify low density lipoproteins, either by a free radical mechanism or by the action of lipoxygenases. Previous studies demonstrated that activated human polymorphonuclear leukocytes can oxidize low density lipoprotein lipids. Stimulation of the cells with phorbol 12-myristate 13-acetate resulted in an increase both in superoxide anion production and in low density lipoprotein oxidation. The present results show that the oxidative modification of low density lipoproteins by human polymorphonuclear leukocytes can be inhibited by superoxide dismutase but not by the lipoxygenase inhibitor, (5,8,11,14)-eicosatetraynoic acid. The low density lipoproteins oxidized by polymorphonuclear leukocytes were recognized by the scavenger receptor of macrophages (P 388 cell line). It is proposed that the superoxide anion is an important factor in the the oxidative modification of low density lipoproteins induced by polymorphonuclear leukocytes, and that under conditions of increased oxidative metabolism in vivo, polymorphonuclear leukocytes can contribute to foam cell formation by a scavenger receptor-dependent process at lesion sites.

Introduction

The pathogenesis of atherosclerosis is complex and multifactorial. Hypercholesterolaemia is widely accepted as one of the major risk factors contributing to the development of coronary heart disease. From epidemiological studies (1, 2) and animal experiments (3, 4) it is clear that cholesterol is deposited in atherosclerotic plaques and that this cholesterol is mainly derived from plasma low density lipoproteins (5, 6). Recent evidence suggests an important role for the oxidative modification of low density lipoproteins in the pathogenesis of atherosclerosis. Incubation of low density lipoproteins with various cells such as endothelial cells, macrophages, human monocytes, and smooth muscle cells leads to an oxidatively modified form which is recognized by the scavenger receptor of macrophages, thus inducing foam cell formation (7). This type of modification is characterized by the peroxidation of low density lipoprotein lipids and the modification of the apolipoprotein B-100 by lipid peroxidation products (8, 9). It has been proposed that the oxidative modification of low density lipoproteins by cells can be mediated either by superoxide anions (10), or by the action of the 15-lipoxygenase enzyme (11, 12).

Leukocytes, both polymorphonuclear neutrophil leukocytes and monocytes, have been observed in the earliest atherosclerotic lesions (13, 14). When they encounter an appropriate ligand, these cells generate highly unstable oxygen species such as superoxide anions, hydrogen peroxide, hydroxyl radicals, and singlet oxygen (15). Increased leukocyte oxidative metabolism has been observed in hyperlipidaemic patients (16), and human polymorphonuclear leukocytes are known to stimulate peroxidation of low density lipoprotein lipids, as measured by the formation of thiobarbituric acid reactive substances and lipid hydroperoxides (17, 18). However, polymorphonuclear

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