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Oxidant Production, oxLDL Uptake, and CD36 Levels in Human Monocyte–Derived Macrophages Are Downregulated by the Macrophage-Generated Antioxidant 7,8-Dihydroneopterin

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Abstract

The severity of atheroma burden in patients strongly correlates to increasing levels of plasma neopterin, the oxidation product of 7,8-dihydroneopterin. Interferon-γ stimulation of macrophages causes the synthesis of 7,8-dihydroneopterin, a potent antioxidant that inhibits oxidative damage to cells, and the cytotoxicity of oxidized low-density lipoprotein (oxLDL) to monocyte-like U937 cells but not THP-1 cells. With human monocyte–derived macrophages (HMDMs), oxLDL triggered a large oxidative stress, causing the rapid loss of cellular glutathione, glyceradehyde-3-phosphate dehydrogenase (GAPDH) inhibition, and eventual loss of viability without caspase-3 activation. Inhibition of oxLDL cytotoxicity to HMDMs occurred at 7,8-dihydroneopterin concentrations $>100\,\mu M$. The oxLDL-mediated glutathione loss and GAPDH inactivation was inhibited by 7,8-dihydroneopterin. 7,8-Dihydroneopterin rapidly entered the HMDMs, suggesting that much of the protective effect was scavenging of intracellular oxidants generated in response to oxLDL. OxLDL uptake by HMDMs was reduced by 30% by 7,8-dihydroneopterin. Immunoblot analysis suggests that this decrease in oxLDL uptake was due to a significant downregulation in the levels of CD36. These results imply that 7,8-dihydroneopterin protects human macrophages both by scavenging oxidants generated in response to oxLDL and by decreasing CD36-mediated uptake of oxLDL. *Antioxid. Redox Signal.* 13, 1525–1534.