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Oxidized Low Density Lipoprotein Cytotoxicity and Vascular Disease

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The formation of oxidized low density lipoprotein (oxLDL) within atherosclerotic plaques is a significant event, which appears to drive the transition from fatty streaks to advanced complex plaque by initiating cell death. OxLDL in tissue culture is a potent cytotoxic agent that triggers a number of competing cell death mechanisms. Oxysterols within oxLDL can alter membrane lipid rafts resulting in calcium influx with calpain activation and cytochrome c release. Apoptosis is also activated by oxysterol-induced degradation of the prosurvival protein kinase, AKT. In contrast, CD36 binding of oxLDL causes necrosis through the generation of an intracellular oxidant flux, while excessive uptake of oxLDL triggers lysosome destabilization. The nature and significance of these mechanisms depends on the type of cell under investigation and how the oxLDL is prepared in the laboratory. Similarly, the endogenous protection mechanisms are also dependent on cell type and the oxLDL preparation. γ-Interferon stimulation of macrophages generates the pterin, 7,8-dihydroneopterin, which inhibits oxLDL toxicity in monocyte-like U937 and human monocyte-derived macrophages, but not the monocyte-like THP-1 cells. Cytotoxic and cellular protection of oxLDL, as well oxLDL formation mechanisms both *in vivo* and *in vitro* will be discussed.

Cholesterol is usually described as the major risk factor for the development of blood clots, high blood pressure, heart disease, and stroke. Yet, it is the oxidation of cholesterol carrying particle in the artery wall which appears to drive much