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Effects of Oxidized LDL in M2 Macrophages: Implications in Atherosclerosis

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Abstract : Introduction: Atherosclerosis is a chronic disease where two striking features are observed: retention of lipids and inflammation. Understanding the interaction between immune cells and lipoproteins involved in atherogenesis are urgent challenges, since cardiovascular diseases are the leading cause of death worldwide. Macrophages are critical to the development of atherosclerotic plaques and in the perpetuation of inflammation in these lesions. These cells are also directly involved in unstable plaque rupture. Recently different populations of macrophages are being identified in atherosclerotic lesions. Although the presence of M2 macrophages (macrophages activated by the alternative pathway, eg. The IL-4) has been identified, the function of these cells in atherosclerosis is not yet defined. M2 macrophages have a high endocytic capacity, they promote remodeling of tissues and to have anti-inflammatory activity. However, in atherosclerosis, especially unstable plaques, severe inflammatory reaction, accumulation of cellular debris and intense degradation of the tissue is observed. Thus, it is possible that the M2 macrophages have altered function (phenotype) in atherosclerosis. Objective: Our aim is to evaluate if the presence of oxidized LDL alters the phenotype and function of M2 macrophages in vitro. Methods: For this, we will evaluate whether the addition of lipoprotein in M2 macrophages differentiated in vitro with IL -4 induces 1) a reduction in the secretion of anti-inflammatory cytokines (CBA and ELISA), 2) secretion of inflammatory cytokines (CBA and ELISA), 3) expression of cell activation markers (Flow cytometry), 4) alteration in gene expression of molecules adhesion and extracellular matrix (Real-Time PCR) and 5) Matrix degradation (confocal microscopy). Results: In oxLDL stimulated M2 macrophages cultures we did not find any differences in the expression of the cell surface markers tested, including: HLA-DR, CD80, CD86, CD206, CD163 and CD36. Also, cultures stimulated with oxLDL had similar phagocytic capacity when compared to unstimulated cells. However, in the supernatant of these cultures an increase in the secretion of the pro-inflammatory cytokine IL-8 was detected. No significant changes where observed in IL-6, IL-10, IL-12 and IL-1b levels. The culture supernatant also induced massive extracellular matrix (produced by mouse embryo fibroblast) filaments degradation. When evaluating the expression of 84 extracellular matrix and adhesion molecules genes, we observed that the stimulation of oxLDL in M2 macrophages decreased 47% of the genes and increased the expression of only 3% of the genes. In particular we noted that oxLDL inhibit the expression of 60% of the genes constituents of extracellular matrix and collagen expressed by these cells, including fibronectin1 and collagen VI. We also observed a decrease in the expression of matrix protease inhibitors, such as TIMP 2. On the opposite, the matricellular protein thrombospondin had a 12 fold increase in gene expression. In the presence of native LDL 90% of the genes had no altered expression. Conclusion: M2 macrophages stimulated with oxLDL secrete the pro-inflammatory cytokine IL-8, have an altered extracellular matrix constituents gene expression, and promote the degradation of extracellular matrix. M2 macrophages may contribute to the perpetuation of inflammation in atherosclerosis and to plaque rupture.

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