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The interaction of native and aggregated LDL with differentially activated human macrophages

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Macrophages are essential cells that participate in tissue homeostasis, initiation and resolution of inflammation, healing processes and removal of endogenous unwanted-self components in pathological conditions. Macrophages are characterized by various phenotypes depending on the microenvironment. Classically activated macrophages polarized by IFNγ mediate host innate immunity and acute inflammation; alternatively activated macrophages differentiated in the presence IL-4 and dexamethasone actively coordinate anti-inflammatory and healing processes. Macrophages express scavenger receptors that mediate recognition, uptake, delivery to endosomes and targeting for lysosomal degradation of unwanted-self ligands by receptor-mediated endocytosis. Stabilin-1 was described in our laboratory as a scavenger receptor expressed on the alternatively activated macrophages. The aims of the present study were to analyze expression of stabilin-1 in the presence of a physiological concentration of glucocorticoids in differentially activated monocyte-derived human macrophages, to analyze the endocytosis of acetylated LDL through the stabilin-1-mediated pathway in differentially activated macrophages, and to investigate the effect of IFNγ on the macrophage endocytic activity, expression of stabilin-1 and its involvement in to endocytic uptake of modified lipoproteins. Using RT-PCR and immunofluorescent staining/confocal microscopy it was found that dexamethasone at the concentration of 10^{-8}M was sufficient for stimulation of stabilin-1 expression. The highest level of stabilin-1 was expressed in IL-4 and dexamethasone stimulated macrophages. However, addition of IFNγ to this combination, despite some suppression of stabilin-1 expression on mRNA level, resulted in the intermediate level of stabilin-1 gene expression that were sufficient for efficient expression of stabilin-1 protein and its partial localization in early endosomes. Using FACS analysis, the quantification of internalized acetylated LDL was analyzed in differentially activated macrophages. The most efficient uptake of acetylated LDL was identified in IL-4 and dexamethasone stimulated macrophages. Addition of IFNγ to this combination significantly reduced, but did not abolish the uptake of acetylated LDL. Using immunofluorescent staining/confocal microscopy, it was demonstrated that IFNγ delayed the intracellular processing of acetylated LDL and limited the recruitment of stabilin-1 during the late stages of endocytosis. The results of the current study demonstrate the recruitment of stabilin-1 in the early endocytic pathway was an essential factor for efficient uptake and degradation of modified lipoproteins. Suppressive effects of IFNγ on the IL-4 and dexamethasone induced stabilin-1 expression and recruitment into the endocytic pathway correlated with the reduced endocytosis of acetylated LDL by macrophages. Our data suggest that IFNγ as a component of the chronic inflammatory microenvironment can suppress the clearance function of macrophages by reducing stabilin-1 levels and changing its intracellular transport. However, even in chronic inflammatory conditions, stabilin-1 can also act as a receptor that mediates the internalization of acetylated LDL and its targeting for degradation.