Minimally modified low density lipoprotein induces macrophage endoplasmic reticulum stress via toll-like receptor 4 and CD36

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Abstract: The minimally modified low density lipoprotein (mm-LDL) induced endoplasmic reticulum stress (ERS) and underlying mechanism was explored in macrophages. RAW264.7 were incubated with mm-LDL (0, 25, 50 and 100 mg/L) for 6, 12 or 24 h. The cellular lipid accumulation was showed by oil red O staining and cholesterol content was quantified by enzymatic colorimetry. The nuclear translocation of activating transcription factor 6 (ATF6) was detected by immunofluorescence assay. The ERS protein markers including phosphorylated inositol-requiring enzyme 1 (p-IRE1), X box binding protein 1 (XBP1) and glucose-regulated protein 78 (GRP78) were detected by Western blotting, and the transcriptional expressions of XBP1 and GRP78 were determined by real time PCR. The results indicated that mm-LDL induced not only a huge accumulation of lipid droplets with increased cholesterol content in the cytoplasm and but also a transport of the Cy3-labeled ATF6, a key component of the unfolded protein response from cytoplasm into nuclei, leading to increased expression of phospho-IRE1, XBP1 and GRP78 in a dose-dependent manner. Pre-incubated with antibodies against TLR4 or CD36 inhibited significantly all mm-LDL stimulated the nuclear translocation of ATF6, the phosphorylation of IRE1, and the up-regulation of the protein and mRNA expression of XBP1 and GRP78 in macrophages. These results suggest that mm-LDL may induce ERS in the dosage dependent way via TLR4 and scavenger receptor CD36 and subsequently activate the unfolded protein response signalling pathway mediated by ATF6 and IRE1 in macrophages.

Key words: endoplasmic reticulum stress; unfolded protein response; macrophage; minimally modified low density lipoprotein; toll-like receptor 4