Intermediate-Density Lipoprotein Is a DNA Synthesis Stimulation Factor in Cultured Human Mesangial Cells

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Dear Sir,

Based on the hypothesis of Moorhead et al. [1], abnormalities of the lipid metabolism are now considered aggravating factors for glomerulonephritis. Low-density lipoprotein (LDL), a cholesterol-rich lipoprotein, attracted attention, initially, and many reports appeared on LDL as a proliferation factor in cultured mesangial cells [2-4]. The presence of LDL receptors and scavenger receptors in mesangial cells has been proved [3, 4], and the uptake of LDL by mesangial cells has been confirmed using an isotope-binding method and the fluorescent antibody technique [3, 5, 6]. It is also known that mesangial cells, with incorporated LDL, secrete various chemical mediators and alter the mesangial microenvironment [7]. For example, there are reports on the expression of messenger RNA of growth factors and cytokines such as platelet-derived growth factor [2] and macrophage chemoattractant protein 1 [8], extracellular matrix such as fibronectin [8] and type IV collagen [9], and eicosanoids such as PG-E2 [4] from mesangial cells when stimulated with LDL or oxidized LDL. A cytotoxic effect of oxidized LDL on mesangial cells and the mechanism of progression to glomerulosclerosis due to this cytotoxicity have been proposed [7, 10]. However, no reports have appeared, as yet, on the action of the triglyceride-rich intermediate-density lipoprotein (IDL) on the mesangial cells. Therefore, we observed the effects on DNA synthesis in mesangial cells stimulated by IDL. The method involved isolation and culture of human mesangial cells as previously

1,400
1,200
1,000
600
400
200
5 10 50 100 500 1,000
IDL (µg/ml)
Fig. 1. Effect of IDL on $[^3H]$thymidine incorporation by mesangial cells. The results represent the $[^3H]$thymidine incorporation per well on 96-well plates. All measurements were carried out in triplicate and expressed as mean ± SE of three experiments. Data were analyzed using analysis of variance. * p < 0.05.

for 48 h. The $[^3H]$TdR uptake by the mesangial cells at each concentration was measured and used as an index of DNA synthesis.

The results showed that DNA synthesis was promoted dose dependently when IDL was added to cultured mesangial cells, up to a level of 5-100 µg/ml, but this promotion was reduced at 500-1,000 µg/ml (fig. 1).

described. Mesangial cells were used between passages 6 and 8. These cells were incubated for 24 h in 0.5% fetal calf serum supplemented medium until the cell growth cycle approached the quiescent phase. After stimulation caused by the addition to a final concentration of 0-1,000 µg/ml of IDL (d = 1.006-1.019), isolated by sequential ultracentrifugation, the cells were then incubated.

These results showed a biphasic pattern, but other researchers [3, 4] have reported that the same pattern was obtained with LDL.

IDL is a very low density lipoprotein (VLDL) remnant obtained when VLDL is acted upon by lipoprotein lipase and also catabolized to LDL by hepatic triglyceride lipase. There is, generally, an increase in remnant lipoprotein, including IDL, in patients with chronic renal failure which is an end stage of chronic glomerulonephritis [11]. It has also been reported that the triglyceride-rich lipoprotein (VLDL+IDL) level in patients with chronic renal failure is about three times higher than in controls [12], and a relationship between triglyceride-rich lipoprotein, such as IDL and chronic renal failure has been suggested.

Remnant lipoprotein is incorporated by macrophages by means of scavenger receptors. They then become foam cells which cause atherosclerosis. The increase in triglyceride-rich apolipoprotein B containing lipoprotein has also been reported to be related to exacerbation of coronary artery disease [13]. It has been reported that hyperlipidemic serum enhances the proliferation of cultured vascular smooth muscle cells [14] and that IDL is considered to be a factor promoting atherosclerosis [15]. There is also an analogy between vascular smooth muscle cells and mesangial cells [16], and it is assumed that IDL is also involved in glomerulonephritis in the same way as it promotes atherosclerosis.

These results show that the triglyceride-rich lipoprotein IDL might be involved in the progression and exacerbation of glomerulonephritis.

References


IDL Is a Stimulating Factor in Mesangial Cells
Nephron 1996;73:334-335