A Secretory Product of Human Monocyte-Derived Macrophages Stimulates Low Density Lipoprotein Receptor Activity in Arterial Smooth Muscle Cells and Skin Fibroblasts

Alan Chait and Theodore Mazzone

The ability of macrophages to influence the metabolism of native low density lipoprotein by arterial smooth muscle cells was evaluated using cultured human monocyte-derived macrophages. Macrophage-conditioned medium stimulated the binding and degradation of low density lipoprotein by cultured arterial smooth muscle cells and skin fibroblasts. Sterol synthesis also was stimulated by macrophage-conditioned medium as was cholesterol esterification in the presence of high concentrations of low density lipoprotein. These findings suggest that macrophages secrete a factor that enhances the activity of the low density lipoprotein receptor. Low density lipoprotein degradation by arterial smooth muscle cells also was enhanced by macrophage-conditioned medium in the presence of high concentrations of low density lipoprotein in the medium. The macrophage factor that stimulates low density lipoprotein metabolism is stable to freezing, is inactivated by acid hydrolysis, trypsic digestion, and boiling, and is of large molecular weight (> 12,000 to 14,000 daltons). Modulation of arterial smooth muscle cell metabolism of low density lipoprotein by a macrophage secretory product may be of importance in the pathogenesis of atherosclerosis. (Arteriosclerosis: 2: 134-141, March/April 1982)

Foam cells in arteriosclerotic plaques appear to derive from two cell types: arterial smooth muscle cells and tissue macrophages. The intracellular lipid that accumulates is predominantly cholesterol ester, the cholesterol component of which is believed to enter cells from plasma. Much recent attention has been directed toward the ability of macrophages in culture to accumulate cholesterol ester after specific receptor-mediated uptake of chemically modified lipoproteins. Unlike human macrophages that have distinct binding sites for both native and modified low density lipoprotein (LDL), arterial smooth muscle cells and other nonmononuclear phagocytic cells lack specific high-affinity binding sites for chemically modified LDL. Therefore, the cholesterol that accumulates in arterial smooth muscle cells is likely to enter cells via the native LDL receptor or other nonreceptor-mediated pathways. Because of the close proximity of smooth muscle cells and macrophages in the arterial wall, the present study was undertaken to determine whether macrophages could influence the metabolism of native LDL by arterial smooth muscle cells in culture.

Macrophages produce a multitude of secretory products with diverse functions. One macrophage secretory product, termed the "macrophage-derived growth factor," is a mitogen that stimulates the proliferation of fibroblasts, arterial smooth muscle cells,
and mouse 3T3 cells in culture.\textsuperscript{10,11} We previously have demonstrated that another mitogen, the platelet-derived growth factor, stimulates receptor-mediated uptake of LDL by arterial smooth muscle cells.\textsuperscript{12} Therefore, the effect of macrophage secretory products on LDL receptor activity and LDL metabolism by cultured arterial cells was tested using macrophage conditioned medium.

Methods

Materials

Sodium \([^{25}S]\)-iodide (carrier-free in 0.1 M NaOH) was purchased from Amersham; 2-[\(\textsuperscript{14}C\)]-acetate, \([\textsuperscript{14}C]\)-oleate, and \([\textsuperscript{3}H]\)-thymidine were purchased from New England Nuclear (Boston, Massachusetts.). Plasmagel was obtained from Roger Bellon Laboratories (Neuilly, France), Ficoll-Hypaque and dextran sulphate from Pharmacia Fine Chemicals (Piscataway, New Jersey); and Dulbecco-Vogt medium, medium RPMI 1640, and trypsin from Grand Island Biological Company (Grand Island, New York). Disposable plastic tissue culture flasks, Petri dishes and filters were purchased from Corning Glassworks, Science Products (Corning, New York), and disposable pipettes from Falcon Labware, Division of Becton, Dickenson and Company (Oxnard, California). Bovine serum albumin was purchased from Miles Laboratories (Elkhart, Indiana), Millipore filters from Millipore Corporation (Bedford, Massachusetts), and nonpolar polycarbonate filters from Biorad-Laboratories (Richmond, California).

Preparation of Human Monocyte-derived Macrophages

We prepared 90\% to 95\% pure human blood monocytes essentially according to Method B of Fogelman et al.,\textsuperscript{13} as described in detail elsewhere.\textsuperscript{14} In brief, healthy donors fasted for 12 to 14 hours overnight after which 120 to 180 ml of blood was drawn into heparinized syringes (5 units/ml). The blood was mixed with Plasmagel in a ratio of 2:1, and after sedimentation of cells for 30 minutes at room temperature, the supernatant plasma was centrifuged for 10 minutes at 400 g, the suspended cell band was removed, and either refrigerated at 4°C or frozen at −20°C. Conditioned media usually were used within 7 days of their being collected.

Culture of Monocyte-Macrophages and Collection of Macrophage-conditioned Medium

In 35 mm tissue culture dishes 0.5–1 $\times 10^6$ monocytes were plated in 1 ml of 20% autologous serum that had not been heat-inactivated, and were placed in a 37°C incubator in humidified 95\% air/5\% CO\(_2\). The cells were fed with 20\% autologous serum 1 day later. Unless otherwise stated, on Day 4 or 5, the cell layer was washed twice with serum-free RPMI 1640 medium, and 1–1.5 ml RPMI 1640 containing 0.2\% bovine serum albumin was added. The macrophage-conditioned medium (MCM) was collected 24 hours later, centrifuged for 10 minutes at 400 g to remove any cellular debris, and the supernatant was decanted and either refrigerated at 4°C or frozen at −20°C. Conditioned media were generally stored at −20°C for up to 6 months.

Culture of Arterial Smooth Muscle Cells and Human Skin Fibroblasts

Procedures described in detail elsewhere\textsuperscript{15} were used to subculture smooth muscle cells from intimal-medial explants of thoracic aortas from pigtail monkeys (\textit{Macaca nemestrina}). Explants and subcultures were grown in modified Dulbecco-Vogt medium containing 5\% pooled monkey blood serum in humidified 95\% air/5\% CO\(_2\). Cells from the second or third subculture were trypsinized and plated at 1.0–1.2 $\times 10^6$ cells in 35 mm dishes in 1.5 ml 5\% monkey plasma-derived serum (PDS). Cells were then fed twice weekly with 5\% PDS.

Human skin fibroblasts, grown from punch skin biopsies of normal volunteers, were explanted and subcultured in modified Dulbecco-Vogt medium containing 10\% pooled human serum, as previously described.\textsuperscript{17} Fibroblasts from the 4th to the 10th subculture were trypsinized, and $5 \times 10^6$ cells were plated in 35 mm dishes in 1.5 ml 10\% pooled human whole blood.
blood serum. The cells were fed twice weekly with 10% whole blood serum.

After 5 to 8 days in culture, the medium was removed from the arterial smooth muscle cells or fibroblasts and replaced with 1 ml RPMI 1640 tissue culture medium containing 0.2% albumin, after the cell layer had been washed twice with serum-free medium. After 24 hours 0.4 to 0.5 ml of medium was removed and replaced by an equal volume of MCM or control medium, prepared identically to the MCM except that it had not been exposed to macrophages. After a further 24 hours, [125I]-LDL, [14C]-acetate, [14C]-oleate, or [3H]-thymidine was added.

**Measurement of LDL Binding and Degradation**

Human LDL (d = 1.019 to 1.063) was prepared by sequential ultracentrifugation from fresh plasma obtained from normal donors. Iodination with [125I] was performed with the iodine monochloride method as modified for lipoproteins, as previously described, to yield specific activities of approximately 100 to 300 cpm/ng. The [125I]-LDL was used within 2 weeks of preparation and was sterilized by passage through a Millipore filter before use.

LDL binding was measured by releasing bound [125I]-LDL from cell surface receptors using dextran sulphate as previously described. Cells were pre-chilled to 4°C. After removing the medium and washing the cell layer, 7.5 µg/ml [125I]-LDL in serum-free medium was added for a 2-hour incubation at 0–4°C. After the cell surface was washed extensively, dextran sulphate (4 mg/ml) was added for 1 hour at 0–4°C. An aliquot of the bound LDL that was released by dextran sulphate was counted in a Packard gamma spectrometer. The cell layer was dissolved in 0.1 M NaOH, and its protein content was determined.

LDL degradation was measured as previously described. [125I]-LDL was added to dishes containing cells to give a final concentration of 7.5 µg/ml unless otherwise stated. Incubations were performed for either 4 or 24 hours at 37°C after which an aliquot of medium was removed for the determination of trichloracetic acid (TCA) soluble [125I] that was not due to free iodide. Non-cell-associated lipoprotein degradation was measured under identical conditions in cell-free dishes and was subtracted from total LDL degradation to give a measure of cellular LDL degradation. Cell number was obtained by counting trypsin-released cells in a hemocytometer; cellular LDL degradation was expressed per 10^6 cells.

**Other Assays**

Sterol synthesis was measured as the incorporation of 2-[14C]-acetate into digitonin-precipitable sterols as previously described. Cells were incubated with [14C]-acetate for 2 hours at 37°C, after which the lipids were extracted from the cell layer by the method of Stein et al. Hydrolysis with 1 M KOH in 95% (vol/vol) ethanol was performed at 85°C for 1 hour. The nonsaponifiable sterols were then precipitated with digitonin, and the [14C] radioactivity in the washed digitonin precipitate was counted in a Packard scintillation counter (Packard Instruments, Downers Grove, Illinois).

Esterification of cholesterol was measured after incubation of cells with [14C]-oleic acid for 2 hours at 37°C in the presence of 200 µg/ml LDL. At the end of the incubation, the cell layer was washed five times with phosphate-buffered saline (PBS), and the cells were harvested and the lipids extracted by the method of Stein et al. Lipids were separated by thin layer chromatography in hexane/diethyl ether/methanol/acetic acid (90:20:3:2, vol/vol). The cholesterol ester spots were visualized using iodine, scraped into scintillation vials, and counted for [14C] radioactivity.

DNA synthesis was measured as the incorporation of [3H]-thymidine into DNA, as described previously. [3H]-thymidine, 2.5 µCi/ml, was added to cells for 2-hour incubation at 37°C. At the end of the incubation, the medium was removed, and the cells were precipitated in situ with 5% TCA. After washing twice with TCA and once with PBS, the cell layer was dissolved in 0.25 M NaOH and an aliquot counted for [3H].

**Results**

MCM stimulated the binding and degradation of [125I]-LDL in quiescent cultured arterial smooth muscle cells that had been grown in PDS (figure 1).

![Figure 1](http://atvb.ahajournals.org/figshare/){figshare}

**Figure 1.** Effect of macrophage-conditioned medium (MCM) on LDL binding and degradation in monkey arterial smooth muscle cells. Arterial smooth muscle cells that were quiescent in 5% plasma-derived serum were washed with serum-free medium and placed in medium containing 0.2% albumin. MCM or an equivalent volume of control medium that had not been exposed to macrophages was added to the cells 24 hours later as described in the methods section. After 24 hours of exposure to the MCM and control media, [125I]-LDL was added for determination of its binding at 4°C, or its degradation at 37°C, over the ensuing 24 hours. Values shown are means ± so from quadruplicate dishes.
In addition to stimulating LDL binding and degradation, MCM also enhanced the synthesis of sterols from [14C]-acetate and the incorporation of [14C]-oleate into cholesterol esters in the presence of high concentrations of unlabeled LDL (Table 1).

To test whether the effect of MCM was to increase the number of LDL receptors or to alter the affinity of LDL for its receptor, LDL degradation was used as a measure of LDL receptor activity at various concentrations of [125I]-LDL (Figure 3). Cells were exposed to MCM for 24 hours before the addition of increasing amounts of [125I]-LDL. At all concentrations of LDL tested, LDL receptor activity was greater in the presence of MCM (Figure 3A). Linearization techniques indicated that the effect of MCM was to increase the apparent "Vmax" from 1.95 to 4.12 μg/10⁶ cells⋅24 hr⁻¹, and to decrease apparent "Km" (6.7 to 2.1 μg/ml) (Figure 3B).

Since LDL receptors in vivo are likely to be down-regulated due to exposure of the cells to high concentrations of LDL in the interstitial fluid, the effect of MCM on LDL degradation in the presence of large amounts of unlabeled LDL was tested. [125I]-LDL degradation in MCM-exposed and control cells was compared in the presence and absence of a 25-fold excess of unlabeled LDL (Table 2). Even in the presence of excess LDL in the medium, LDL degradation was enhanced by MCM.

Since diabetics are more prone to develop atherosclerotic complications than are nondiabetics, the potential role of glucose and insulin in stimulating the production of the factor in MCM that stimulates LDL receptor activity was evaluated. To study the effects of the glucose concentration to which the macrophages were exposed, macrophages were plated and cultured either in 0, 100 or 500 mg/dl glucose. MCM also was collected at these glucose concentrations. No effect of glucose, either during the growth of the macrophages or during the period of harvesting the conditioned medium, was observed with respect to stimulation of LDL degradation in recipient fibroblasts (Figure 4A). To evaluate the effect of insulin, macrophages were grown and MCM was collected either with no added insulin or in the presence of insulin added to concentrations of 100, 1000, and 10,000 μU/ml. Since these conditioned media

Table 1. Effect of Macrophage-Conditioned Medium (MCM) on Low Density Lipoprotein (LDL) Receptors, Sterol Synthesis, and Cholesterol Esterification by Arterial Smooth Muscle Cells

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MCM</th>
<th>% Stimulation by MCM</th>
</tr>
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<tbody>
<tr>
<td>LDL binding (ng/mg protein)</td>
<td></td>
<td>14.7 ± 1.5</td>
<td>76.6 ± 5.7</td>
</tr>
<tr>
<td>Sterol synthesis (cpm/mg protein • hr⁻¹)</td>
<td></td>
<td>1783 ± 388</td>
<td>4089 ± 664</td>
</tr>
<tr>
<td>Cholesterol esterification* (nmole/mg protein • hr⁻¹)</td>
<td></td>
<td>0.86 ± 0.05</td>
<td>1.18 ± 0.04</td>
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Values shown are means ± so from quadruplicate dishes.

*Cholesterol esterification was measured in the presence of 200 μg/ml unlabeled LDL.
Figure 3. Effect of macrophage-conditioned medium (MCM) on LDL receptor activity. Quiescent cells were obtained as described in figure 1. MCM (•) or control media (○) was added to the cells, and 24 hours later [125I]-LDL was added at the concentrations indicated for measurement of LDL degradation over the ensuing 24 hours. A. [125I]-LDL saturation curves. B. Linearization plot\(^2\) of the data in A. The slope of the line = apparent "Vmax" and the point of intersection with the y axis = "- Km." Means of quadruplicate measurements are shown.

contain insulin, control recipient cells also were exposed to MCM that had been harvested in the absence of insulin, but to which insulin had been added directly. Arterial smooth muscle cells were chosen as the recipient cells for this experiment because LDL receptor activity in this cell type does not appear to be stimulated by insulin as occurs with cultured skin fibroblasts.\(^1\) At all insulin concentrations, MCM resulted in greater LDL degradation by arterial smooth muscle cells than did medium not previously conditioned by macrophages. However, insulin, whether added to the macrophages or directly to the recipient cells, had no additional effect (figure 4 B).

The monocyte-macrophages used in all these experiments were not stimulated other than by their spreading and attachment to the plastic tissue culture dish. To determine whether additional stimulation of the macrophages would result in an increased stimulatory activity of the MCM on recipient cells, bacterial endotoxin and zymozan were used to stimulate the macrophages during the collection of the conditioned medium. MCM collected in the presence

<table>
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<tr>
<th>[129I]-LDL degradation* (ng/10⁶ cells - 24 hr⁻¹)</th>
<th>Control</th>
<th>MCM</th>
<th>% Stimulation by MCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No unlabeled LDL added</td>
<td>216 ± 22</td>
<td>2474 ± 148</td>
<td>1045</td>
</tr>
<tr>
<td>In presence of 25-fold excess of unlabeled LDL †</td>
<td>56.5 ± 2.5</td>
<td>85.7 ± 3.6</td>
<td>52</td>
</tr>
</tbody>
</table>

Values shown are means ± sd from quadruplicate dishes.

*7.5 μg [129I]-LDL was added for the measurement of LDL degradation.

†Unlabeled LDL was added to the cells at the same time as the MCM. Thus, the cells were exposed to the excess and unlabeled LDL both during the preincubation with MCM and during the subsequent incubation with [129I]-LDL.
of these two substances did not stimulate LDL degradation in recipient cells to a substantially greater extent than when collected in their absence (table 3).

Human monocyte-macrophages recently have been reported to secrete a mitogen, the macrophage-derived growth factor. Since other mitogens can affect LDL receptor activity, the effect of MCM on LDL degradation and DNA synthesis was tested concurrently. [3H]-LDL or [3H]-thymidine were added to arterial smooth muscle cells that had been exposed to MCM for the previous 24 hours. Although LDL degradation was enhanced by MCM, DNA synthesis was not stimulated (figure 5) using identical

![Figure 4](image_url)

**Figure 4.** Effect of glucose (A) and insulin (B) on monocyte-derived macrophages (MCM)-induced stimulation of LDL degradation. MCM were plated in medium containing 20% autologous serum as described in Methods. The glucose concentration used for culture (numerator) and for MCM collection (denominator) was varied and tested for its effect on LDL degradation in recipient cells. To test the effect of insulin, macrophages were grown in medium containing 20% autologous serum to which different amounts of insulin were added. Recipient fibroblasts (A) or quiescent arterial smooth muscle cells (B) were exposed to MCM (hatched bars) or control media (open bars) at the designated concentrations of glucose (A) or insulin (B). In addition, insulin was added at the concentration illustrated to MCM that had been collected without added insulin (B, solid bars). No effect of either glucose or insulin was demonstrable.

![Figure 5](image_url)

**Figure 5.** Lack of effect of macrophage-conditioned medium (MCM) on DNA synthesis. MCM was collected as described in Methods and exposed to recipient quiescent arterial smooth muscle cells for 24 hours as described in the legend to figure 1. Then either [3H]-LDL or [3H]-thymidine was added to arterial smooth muscle cells that had been exposed to MCM for the previous 24 hours. Although LDL degradation was enhanced by MCM, DNA synthesis was not stimulated (figure 5) using identical

<table>
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<tr>
<th>Activator</th>
<th>LDL degradation (% of values in ASMCs not exposed to MCM)</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>202 211 158 166</td>
</tr>
<tr>
<td>Bacterial endotoxin</td>
<td>238 201 169 190</td>
</tr>
<tr>
<td>Zymozan</td>
<td>233 230 165 205</td>
</tr>
</tbody>
</table>

*Bacterial endotoxin (25 µg/ml) or opsonized zymozan (1 mg/ml) was added at the time that the medium was changed from autologous serum to 0.2% albumin containing serum-free medium.

†Values for LDL degradation in control dishes not exposed to MCM were 2.45 ± 0.37 µg/10^6 cells • 24 hr ^{-1}. For each condition, quadruplicate values were obtained. The results are expressed as percent of the values in the cells not exposed to MCM.

‡MCM in 0.2% BSA was collected for either 3 hours (0–3 hr) or 24 hours (0–24 hr) after the macrophages had been in culture in 20% autologous serum for 1 or 4 days.

§Values in parenthesis represent the percent of values obtained in the absence of activators.
conditions that previously resulted in stimulation of LDL degradation in monkey arterial smooth muscle cells by platelet-derived growth factor.12

Studies performed to characterize the factor in MCM that stimulates LDL receptor activity showed that the factor is stable to freezing, and to exposure to a temperature of 56°C for 30 minutes, but that a large proportion of its activity (72%) is lost by boiling (table 4). Activity also is substantially reduced by treatment with 6 N HCl, but not with 1 N HCl (data not shown), by trypsin digestion, and by filtration across a millipore filter. However, filtration across a nonpolar polycarbonate filter did not reduce the stimulatory effect of MCM on LDL degradation to a similar extent. Dialysis through a membrane that excludes particles of 12,000 to 14,000 daltons did not reduce the activity of the MCM.

Discussion

A unique feature of macrophages is that they elaborate a wide range of secretory products with diverse functions. This study provides evidence that macrophages also secrete a factor that can stimulate LDL receptor activity in cultured arterial smooth muscle cells and skin fibroblasts. Exposure of cells to macrophage-conditioned medium leads to an increase in the binding and degradation of LDL, and stimulates sterol synthesis. This suggests that the factor that is secreted by these cells leads to enhanced binding of LDL to its receptor, with subsequent enhanced uptake and degradation of the lipoprotein. The basal amount of LDL binding and degradation observed was low, presumably because the cells had been made quiescent before treatment with the MCM.

Results of experiments using increasing amounts of [125I]-labeled LDL in recipient cells exposed either to MCM or control media suggest that an effect of this macrophage factor is to increase the number of LDL receptors, although enhanced affinity of LDL for its receptor also appears to play a role in the increased LDL receptor activity observed. Despite the fact that many proteases are secreted by macrophages,9 the macrophage product responsible for stimulating LDL degradation by cells did not result in enhanced LDL degradation in a cell-free system.

Since cells in vivo normally are exposed to much higher concentrations of LDL than used in these LDL binding and degradation studies, for MCM stimulation of LDL transport to be of potential significance in vivo, it would be necessary for this effect to be present with high concentrations of LDL in the incubation medium. This indeed is the case, since [125I]-LDL degradation was enhanced even in the presence of 200 μg/ml of LDL protein, and cholesterol esterification also was stimulated to a similar extent in the presence of high levels of unlabeled LDL in the medium. The increased degradation in the presence of unlabeled LDL could be due to an increase in the basal LDL receptor activity, fluid phase pinocytosis, or low affinity LDL uptake. However, since MCM-treated cells show the same slope for [125I]-LDL degradation as the controls at [125I]-LDL levels above saturation for the receptor, the increase in LDL degradation elicited by MCM in the presence of unlabeled LDL appears to be due to an increase in LDL receptors. Thus, it is possible that LDL flux through cells could be accelerated in vivo, especially since it is now believed that LDL receptors, even though down-regulated, are important in regulating the delivery of cholesterol; and that this process can be regulated by environmental influences, such as hormones.25

Although another macrophage factor, macrocor- tin, appears to be regulated by glucose concentration,26 the elaboration of the macrophage secretory product responsible for stimulating LDL receptor activity was not regulated either by glucose or by insulin. Also, stimulation of the macrophages by both bacterial endotoxin and zymozan failed to affect the production of this factor.

The factor secreted by macrophages that stimulates LDL receptor activity in arterial smooth muscle cells and fibroblasts is of large molecular weight, since it was retained by dialysis using membranes that exclude particles of greater than 12,000 to 14,000 daltons. The factor appears to be a protein in that its activity can be destroyed by trypsin digestion, acid treatment, and partly by boiling. It is stable to freezing and gentle acid hydrolysis and sticks readily to millipore filters, suggesting that it is a highly charged molecule. The relationship between this factor and the macrophage-derived growth factor is not clear. MCM did not stimulate DNA synthesis by quiescent arterial smooth muscle cells using identical conditions that result in its stimulation by platelet-derived growth factor.10,11

Table 4. Effects of Various Treatments on the Ability of Macrophage-Conditioned Medium (MCM) to Stimulate LDL Receptor Activity in Arterial Smooth Muscle Cells

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL degradation (% reduction*)</th>
</tr>
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<tbody>
<tr>
<td>56°C for 30 minutes</td>
<td>15</td>
</tr>
<tr>
<td>100°C for 3 minutes</td>
<td>72</td>
</tr>
<tr>
<td>Freezing</td>
<td>−14</td>
</tr>
<tr>
<td>6 N HCl</td>
<td>103</td>
</tr>
<tr>
<td>Dialysis (12–14 K dalton)</td>
<td>−10</td>
</tr>
<tr>
<td>Trypsinization</td>
<td>57</td>
</tr>
<tr>
<td>Filtration: millipore filter</td>
<td>82</td>
</tr>
<tr>
<td>filtration: nonpolar filter</td>
<td>31</td>
</tr>
</tbody>
</table>

*Calculated as:

\[
\frac{\text{MCM (untreated)} - \text{MCM (treated)}}{\text{MCM (untreated)}} \times 100.
\]
derived growth factor, and bacterial endotoxin stimulation was without additional effect on LDL receptor activity, yet markedly enhanced the secretion of the macrophage-derived growth factor. Further studies need to be carried out to determine whether the factor in our conditioned medium that stimulates LDL degradation is indeed the macrophage-derived growth factor.

The macrophage is reemerging as a cell of major importance in the genesis of atherosclerotic lesions. Macrophages appear to be precursors of foam cells and appear capable of accumulating cholesterol esters when exposed to chemically modified lipoproteins, some of which may occur naturally. Also, the secretory potential of these cells may be important in the pathogenesis of atherosclerosis. In addition, stimulation of LDL flux through adjacent arterial smooth muscle cells beyond the capacity of the cell to use or remove the cholesterol could result in cholesterol ester accumulation and foam cell formation in arterial smooth muscle cells.

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References

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A Chait and T Mazzone

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