Synergistic Effects of Growth Factors on the Regulation of Smooth Muscle Cell Scavenger Receptor Activity*

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Rabbit smooth muscle cells (SMC) express types I and II scavenger receptors (ScR) that are up-regulated by platelet secretion products. In the current studies we investigated the effect of growth factors secreted by platelets on ScR activity in rabbit and human SMC. Platelet-derived growth factor (PDGF BB) and transforming growth factor β1 (TGF-β1) at 10 ng/ml increased ScR activity in rabbit SMC (by approximately 4- and 2-fold, respectively) but not in human SMC. Epidermal growth factor (EGF) or insulin-like growth factor I (IGF-I) alone had little effect on SMC ScR activity. The growth factors had synergistic effects on ScR activity and on types I and II ScR mRNA expression. In rabbit SMC, PDGF BB, EGF, and TGF-β1 together stimulated ScR activity 12-fold. In human SMC, EGF and TGF-β1, together with either IGF-I or PDGF BB, stimulated receptor activity approximately 7-fold. Growth factor-mediated induction of ScR activity in rabbit and human SMC was blocked by the tyrosine kinase inhibitor tyrphostin 47, whereas the induction of ScR activity in rabbit but not human SMC was blocked by the protein kinase C inhibitor MDL 29,152. Studies using neutralizing antibodies demonstrated that TGF-β1 is the predominant factor in in vitro preparations of platelet secretory products which regulates ScR activity. The growth factors that act synergistically in regulating ScR activity in vitro are all present in atherosclerotic lesions, where they are produced by macrophages, endothelial cells, SMC, and platelets. The data suggest that these growth factors may regulate ScR activity in SMC in vivo and contribute to foam cell formation.

One characteristic feature of atherosclerotic lesions is the unregulated accumulation of lipoprotein-derived cholesterol and cholesteryl esters in macrophages and smooth muscle cells of the arterial intima. Lipid is deposited in these cells as droplets that give the cells a foamy appearance when viewed by phase-contrast microscopy (1–4). The mechanism of lipid accumulation and foam cell formation is not known with certainty; however, lipid accumulation in macrophages has been postulated to result from the scavenger receptor-mediated internalization of modified lipoproteins (5–8). We have demonstrated recently that smooth muscle cells also express scavenger receptors, and we have postulated a similar mechanism for lipid accumulation in these cells (9–12).

The expression of the scavenger receptor in both macrophages and smooth muscle cells can be induced during atherogenesis. Whereas circulating monocytes do not express scavenger receptors, scavenger receptor expression is induced to high levels when the monocytes adhere to the endothelium, penetrate between the endothelial cells, and differentiate to macrophages in the subendothelial space (2, 4, 13, 14). During atherogenesis, smooth muscle cells migrate from the media to the intima of the arterial wall, where they proliferate and accumulate lipid, becoming foam cells. Scavenger receptor activity is detected in smooth muscle cells in the intima but not in normal vascular smooth muscle cells (15–17), demonstrating that smooth muscle cell scavenger receptor activity is up-regulated in atherosclerotic lesions. The factors contributing to the regulation of smooth muscle cell scavenger receptor activity in vivo are unknown.

We have shown that scavenger receptor activity in rabbit smooth muscle cells is induced in vitro by incubation of the cells with phorbol esters, serum, or secretion products from platelets (10). The expression of types I and II scavenger receptors in smooth muscle cells is normally quite low; however, incubation of the cells with phorbol esters increases receptor activity up to 20-fold (10–12). Types I and II scavenger receptor cDNAs have been cloned from a cDNA library prepared from phorbol ester-treated rabbit smooth muscle cells (18). Incubation of rabbit smooth muscle cells with secretion products from human platelets, stimulated with thrombin or with the calcium ionophore A23187, also results in up to a 5- to 6-fold increase in receptor activity (10–12). These data suggest that platelet secretory products present in serum or at sites of platelet aggregation may contribute to the regulation of smooth muscle cell scavenger receptor activity.

In the present studies we examined the effect of several known platelet secretory products on scavenger receptor activity in human and rabbit smooth muscle cells. The results demonstrate that platelet-derived growth factor (PDGF) BB, epidermal growth factor (EGF), insulin-like growth factor I (IGF-I), and transforming growth factor β1 (TGF-β1), growth factors present in atherosclerotic lesions (19–23), synergistically stimulate types I and II scavenger receptor gene expression and receptor activity in both human and rabbit smooth muscle cells.

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1 The abbreviations used are PDGF, platelet-derived growth factor; EGF, epidermal growth factor; IGF-I, insulin-like growth factor I; TGF-β1, transforming growth factor β1; DiI, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate; LDL, low density lipoproteins; Ac-LDL, acetyl low density lipoproteins; FACS, fluorescence-activated cell sorter; TNF-α, tumor necrosis factor α; IFN-γ, interferon-γ.
EXPERIMENTAL PROCEDURES

Materials—Heat-inactivated fetal bovine serum was obtained from HyClone Laboratories (Logan, UT). Dulbecco's modified Eagle's medium, Dulbecco's phosphate-buffered saline, penicillin, and streptomycin were obtained from Life Technologies, Inc. Two human aortic smooth muscle cell lines and growth medium with (SmGM 2) or without (SmBM) serum were purchased from Clonetics (San Diego). Serotonin, fibronectin, and fibrinogen were purchased from Sigma. Human recombinant IGF-I, PDGF, and TGF-β1 were purchased from Promega (Madison, WI). Tyrphostin 47 and tyrphostin 1 were purchased from the Marion Merrell Dow Research Institute (Cincinnati, OH) (24). Fresh human platelet-rich plasma was obtained from the Peninsula Blood Bank (San Mateo, CA). The fluorescent probe, 1,1'-dioctadecyl-3,3',3'-tetramethylindocarbocyanine perchlorate (DiI) was purchased from Molecular Probes, Inc. (Eugene, OR). Sodium [125I]iodide was purchased from Amersham Corp.

To neutralize their activity, platelet secretory products (40–60 μg/ml) were added in combination, synergistic effects were observed. The growth factors IGF-I and PDGF BB alone had little effect on receptor activity, whereas preincubation with the combination of the four growth factors significantly enhanced the uptake of DiI-labeled Ac-LDL by both rabbit and human smooth muscle cells (data not shown).

To obtain a quantitative estimate of the increase in receptor activity induced by the growth factors and to assess the effect of each growth factor individually, additional experiments were performed. The cells were preincubated with the recombinant growth factors either alone or in combination, and the uptake of DiI-labeled Ac-LDL was assessed by FACS analysis. When DiI-labeled lipoproteins are internalized by cells and degraded, the DiI is quantitatively retained in the lysosomes. The amount of DiI in the cells is therefore directly proportional to the amount of lipoprotein metabolized (28). In rabbit smooth muscle cells (Fig. 1A), PDGF BB (10 ng/ml) stimulated the internalization of DiI-labeled Ac-LDL by 3.7-fold, whereas neither PDGF AA (10–70 ng/ml) nor PDGF AB (10–70 ng/ml) had any effect on the uptake of DiI-labeled Ac-LDL (data not shown). TGF-β1 (10 ng/ml) up-regulated scavenger receptor activity 2-fold. The growth factors IGF-I (20 ng/ml) or EGF (10 ng/ml) had little effect on receptor activity when added to cells alone at the concentrations shown here or at concentrations up to 100 ng/ml (data not shown). However, when these growth factors were added in combination, synergistic effects were observed. The four combinations, IGF-I and TGF-β1, PDGF BB and EGF and TGF-β1, stimulated receptor activity to a significantly greater extent than that observed with any growth factor alone. The greatest synergistic effect with two growth factors was with EGF and TGF-β1, in which receptor activity was increased 7.5-fold. An even greater increase in receptor activity (12-fold) was observed with a combination of the three growth factors EGF, TGF-β1, and PDGF BB. Addition of IGF-I with the three growth factors had little, if any, additional effect on receptor activity.

In human smooth muscle cells the growth factors also had synergistic effects on scavenger receptor activity (Fig. 1B). Whereas IGF-I, EGF, TGF-β1, and PDGF BB alone had little effect on receptor activity, EGF and TGF-β1 together had a substantial effect, up-regulating receptor activity approximately 3.4-fold. The addition of either IGF-I or PDGF BB, together with these two growth factors, increased receptor activity up to 7-fold. The addition of a fourth growth factor had no additional stimulatory effect. A similar effect of the combination of growth factors was obtained with a second human aortic...
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smooth muscle cell line (data not shown). The growth factors, therefore, had similar effects on human and rabbit smooth muscle cell scavenger receptor activity, except that PDGF was more potent in the rabbit cells, and IGF-I had more of an effect in the human cells.

The effect of the recombinant growth factors on the internalization of both Ac-LDL and native LDL by rabbit and human smooth muscle cells was examined to determine if the regulation of receptor activity was specific for the scavenger receptor or if LDL receptor activity was also increased. In rabbit smooth muscle cells scavenger receptor activity was stimulated by the mixture of the four growth factors (PDGF BB, EGF, TGF-β1, and IGF-I), whereas LDL receptor activity was not increased (Fig. 2A). In contrast, in human smooth muscle cells, the uptake of both Ac-LDL and native LDL was up-regulated by the combination of the four growth factors (Fig. 2B).

Whereas the internalization of Dil-labeled Ac-LDL has been shown to be proportional to the amount of Ac-LDL internalized and degraded in other systems, it was important to determine directly whether the enhanced uptake of Dil-labeled Ac-LDL induced by the growth factors also led to increased lipoprotein metabolism in these studies. For this purpose, the smooth muscle cells were pretreated with the combination of the four growth factors, and the effect on the metabolism of 125I-Ac-LDL was determined. The degradation of 125I-Ac-LDL was enhanced 3.8-fold in human smooth muscle cells incubated with the growth factors at 37°C for 16 h, and the cellular association of 125I-Ac-LDL, which represents bound and internalized 125I-Ac-LDL, was enhanced 2.9-fold (data not shown). These data therefore confirm the results of the FACS analysis (Fig. 1B) and demonstrate growth factor-mediated enhanced internalization and degradation of Ac-LDL by human smooth muscle cells. Similar results were obtained in rabbit smooth muscle cells (data not shown).

Previously we have shown that expression of types I and II scavenger receptor was increased by phorbol ester treatment of rabbit smooth muscle cells (11, 12). To determine whether the enhancement of scavenger receptor activity by these growth factors is due to an induction of types I and II scavenger receptor expression, we performed RNase protection assays to examine scavenger receptor mRNA levels using a probe specific for both the types I and II isoforms. In this particular study scavenger receptor mRNA was not detected in rabbit smooth muscle cells under basal tissue culture conditions (Fig. 3). However, treatment of the smooth muscle cells with the combination of the four growth factors for 16 h increased the expression of both types I and II scavenger receptor mRNA. Similar induction of scavenger receptor mRNA expression was observed in human smooth muscle cells (data not shown).

To determine the mechanism of growth factor stimulation, we first tested the effect of a tyrosine kinase inhibitor on the stimulatory effect of the growth factors on scavenger receptor activity. Incubation of rabbit smooth muscle cells with growth factors led to a 12-fold increase in scavenger receptor activity that was essentially abolished by tyrphostin 47, a tyrosine kinase inhibitor (Table I). Tyrphostin 1, an inactive analog of tyrphostin 47, had little effect. In human smooth muscle cells the growth factor-induced increase in receptor expression was also blocked by tyrphostin 47 (Table I). These data demonstrate that the growth factor-mediated induction of scavenger receptor activity in both rabbit and human smooth muscle cells
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**TABLE I**

| Treatment                      | Fold increase in receptor activity |
|--------------------------------|-----------------------------------|
| Rabbit smooth muscle cells     | Human smooth muscle cells          |
| Growth factors alone           | 11.9 ± 0.5                        |
| Growth factors + tyrophostin 47| 1.9 ± 0.2                         |
| Growth factors + tyrophostin 1 | 10.3 ± 0.2                        |
| Growth factors + MDL-29,152    | 0.6 ± 0.1                         |

*Effects of the tyrosine kinase inhibitor tyrophostin 47 and the protein kinase C inhibitor MDL-29,152 on the growth factor-mediated regulation of scavenger receptor activity in smooth muscle cells.*

The cells were preincubated (as described in the legend to Fig. 1) with a mixture of EGF, PDGF BB, IGF-I, and TGF-β1, alone or together with tyrophostin 47, a tyrosine kinase inhibitor (50 μM), tyrophostin 1, an inactive analog of tyrophostin 47 (50 μM), or MDL-29,152, a protein kinase C inhibitor (100 μM). Receptor activity was then assessed by examining the uptake of Dil-labeled Ac-LDL as described in the legend to Fig. 1. The data are reported as the fold increase in receptor activity (mean ± range for two independent experiments) over the activity observed in the absence of the growth factors.

Our data clearly demonstrate that PDGF BB, EGF, IGF-I, and TGF-β1, in combination synergistically stimulate scavenger receptor activity in smooth muscle cells. We next performed experiments to determine whether these growth factors are the components in our preparation of platelet secretory products responsible for stimulation of scavenger receptor activity. We first estimated the amount of the four growth factors present in platelet secretory products using Western blot analysis. The platelet secretory products contained approximately 0.35 ng of TGF-β1, 0.11 ng of PDGF, and less than 0.03 ng of EGF and IGF-I (Table II). Therefore, 40 μg of platelet secretory products, the level that gave maximum stimulation of scavenger receptor activity, contained ~4.4 ng of PDGF, ~14 ng of TGF-β1, and less than 1 ng each of EGF and IGF-I. We next performed neutralization experiments to determine whether these growth factors play any functional role in mediating the stimulatory effect of platelet secretory products on scavenger receptor activity. As shown in Fig. 4, an anti-PDGF antibody, used at a concentration sufficient to block the effect of recombinant PDGF BB, did not block the stimulatory effect of platelet secretory products on scavenger receptor activity. Antibodies specific for EGF and IGF-I also had little effect. Anti-TGF-β1 antibody, on the other hand, blocked the stimulatory effect of platelet secretory products by ~70%, suggesting that TGF-β1 is one of the active components in platelet secretory products. However, approximately 30% of the stimulatory activity remained, and the addition of anti-PDGF and anti-TGF-β1 together or the addition of a mixture of the four antibodies did not result in a greater inhibition of the stimulatory effect than that observed with anti-TGF-β1 alone. These data indicate that TGF-β1 is responsible for 70% of the stimulatory effect of platelet secretory products on scavenger receptor activity and that the remaining 30% of the activity is not mediated by the growth factors tested.

Two additional experiments support the conclusion that PDGF is not the active component in platelet secretory products. First, when 4.4 ng of recombinant PDGF BB (the amount of PDGF estimated to be present in 40 μg of platelet secretory products, which gives maximum stimulation of receptor activity) was used to treat the rabbit smooth muscle cells, it failed to stimulate scavenger receptor activity, indicating that the amount of PDGF in 40 μg of platelet secretory products is too low to be responsible for the effect of platelet secretory products in our in vitro studies (see Fig. 5). Second, an antagonist to PDGF (Trapidil, 100 μg/ml) which blocked the effect of recombinant PDGF (50 ng/ml) (33) failed to block the stimulatory effect of platelet secretory products on scavenger receptor activity (data not shown). We also tested the ability of recombinant TGF-β1 (14 ng) and PDGF (4.4 ng) (the amounts present
pretreated with 40 μg of platelet secretory products in the absence or presence of blocking antibodies against PDGF (33 μg/ml), EGF (13 μg/ml), IGF-I (10 μg/ml), and TGF-β1 (6 μg/ml) for 16 h at 37°C and then assayed for their ability to internalize DiI-labeled AC-LDL. The data are reported as the mean ± the range for two independent experiments.

![Fig. 4: Ability of blocking antibodies to neutralize the stimulatory effect of platelet secretory products on scavenger receptor activity](image)

FIG. 4. Ability of blocking antibodies to neutralize the stimulatory effect of platelet secretory products on scavenger receptor activity. Smooth muscle cells (SMC) were preincubated with 40 μg of platelet secretory products in the absence or presence of blocking antibodies against PDGF (33 μg/ml), EGF (13 μg/ml), IGF-I (10 μg/ml), and TGF-β1 (6 μg/ml) for 16 h at 37°C and then assayed for their ability to internalize DiI-labeled AC-LDL. The data are reported as the mean ± the range for two independent experiments.

![Fig. 5: Effect of platelet secretory products, PDGF BB, and TGF-β1 alone or in combination on scavenger receptor activity in rabbit smooth muscle cells (SMC)](image)

FIG. 5. Effect of platelet secretory products, PDGF BB, and TGF-β1 alone or in combination on scavenger receptor activity in rabbit smooth muscle cells (SMC). Smooth muscle cells were pretreated with 40 μg/ml of platelet secretory products (PSP) or with either recombinant PDGF BB or TGF-β1, alone or together, at the concentrations indicated, for 16 h at 37°C and then assayed as described in Fig. 1.

in the maximally active concentration of platelet secretory products) alone and together to up-regulate scavenger receptor activity (Fig. 5). Neither TGF-β1 nor PDGF alone or in combination increased receptor activity to the level obtained with the platelet secretory products, again suggesting that there are other factors besides TGF-β1 in platelet secretory products which increase receptor activity either alone or in combination with TGF-β1.

### DISCUSSION

We have shown previously that types I and II scavenger receptor activity in rabbit smooth muscle cells can be up-regulated by phorbol esters, platelet secretory products in serum, and secretion products from activated platelets (10–12). In addition, it has been reported that tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) increase scavenger receptor activity in rabbit smooth muscle cells (17). In the current studies we demonstrated that growth factors stimulate scavenger receptor activity in both human and rabbit smooth muscle cells. PDGF BB and TGF-β1 increased scavenger receptor activity approximately 4- and 2-fold, respectively, in rabbit smooth muscle cells but not in human smooth muscle cells. EGF or IGF-I, when used alone, had little effect on scavenger receptor activity in either human or rabbit smooth muscle cells. However, when incubated with the cells in combination, these growth factors showed synergistic effects on scavenger receptor activity. In rabbit smooth muscle cells PDGF BB and either EGF or TGF-β1, and EGF together with TGF-β1, had synergistic effects in raising scavenger receptor activity, and the addition of all three growth factors together increased receptor activity 12-fold. In human smooth muscle cells EGF and TGF-β1 clearly had a synergistic effect on the induction of scavenger receptor activity, and the addition of either IGF-I or PDGF BB together with these two growth factors increased receptor activity up to 7-fold. We demonstrated that the increase in scavenger receptor activity in both rabbit and human smooth muscle cells by the growth factors is correlated with an increase in type I and II scavenger receptor mRNA expression. We have shown previously that the scavenger receptor expressed by the smooth muscle cells had properties essentially identical to those of the bovine macrophage types I and II scavenger receptors (11, 12).

In rabbit smooth muscle cells the growth factors specifically increased scavenger receptor activity with no effect on LDL receptor activity. In striking contrast to this, in human smooth muscle cells both scavenger receptor and LDL receptor activities were increased. Other investigators have demonstrated previously that growth factors (such as TGF-β and PDGF) stimulate LDL receptor activity in human smooth muscle cells (34, 35). The reasons for the difference in regulation of LDL receptor activity in the rabbit and human smooth muscle cells remain to be determined; however, they could be related to differences in the signal transduction pathways in the rabbit and human cells or to differences in transcription factor binding sites in the human and rabbit LDL receptor genes.

Our results concerning regulation of scavenger receptor activity by growth factors differ slightly from those of Inaba et al. (36, 37), in which they observed a stimulatory effect of PDGF BB or EGF alone on scavenger receptor activity in human smooth muscle cells. We noted a slight stimulatory effect of PDGF BB alone but did not see an effect of EGF alone in two lines of human smooth muscle cells. The difference in these results may be related to the difference in experimental conditions or may simply reflect differences in the properties of various lines of human smooth muscle cells.

Whereas scavenger receptor activity in smooth muscle cells is regulated over a wide range, in differentiated macrophages scavenger receptor activity can be regulated in a narrow range by various growth factors and cytokines. Incubation of macrophages with macrophage colony-stimulating factor results in an increase in scavenger receptor activity (38), whereas incubation of macrophages with TGF-β2 (39), IFN-γ (40–42), and TNF-α (43) reduces receptor activity. The reason for the differential effects of IFN-γ, TNF-α, and TGF-β1 on scavenger receptor activity in smooth muscle cells and macrophages is unknown. The regulation of scavenger receptor activity in smooth muscle cells and macrophages, however, is fundamentally different. In macrophages scavenger receptor expression is constitutively stimulated, and they express a high level of receptor activity. In smooth muscle cells scavenger receptor expression is low in the absence of stimulation.

As we have shown, platelet secretory products regulate scavenger receptor activity in smooth muscle cells. Platelet secretory products can also affect scavenger receptor activity in...
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macrophages. It has been reported that activated platelets secrete a protein-like factor that stimulates scavenger receptor activity in macrophages (44) and that platelets secrete a ligand for the scavenger receptor which competitively inhibits the binding of modified LDL to the scavenger receptor (45, 46). Several platelet secretory products, including serotonin, fibrinogen, fibronecin, and PDGF, inhibit scavenger receptor activity in human monocyte-derived macrophages (47). The current data demonstrating that growth factors present in platelet secretory products stimulate scavenger receptor activity in smooth muscle cells suggest that platelets in atherosclerotic lesions could modulate lipid accumulation in both smooth muscle cells and macrophages.

The recent studies of Li et al. (17) demonstrate that after balloon injury, the aorta smooth muscle cells in the neointima of hypercholesterolemic rabbits express scavenger receptors, whereas smooth muscle cells in the media do not. These data clearly demonstrate that scavenger receptor expression is up-regulated in smooth muscle cells in atherosclerotic lesions. The factors leading to scavenger receptor regulation in smooth muscle cells in vivo are unknown. However, following deendothelialization induced by balloon injury, extensive platelet deposition would occur, making growth factors secreted by activated platelets available to regulate scavenger receptor activity (48–50). In fact, platelets are not the only source of growth factors for the scavenger receptor which competitively inhibits the scavenger receptor-mediated uptake of modified LDL by smooth muscle cells may also lead to lipid accumulation and foam cell formation in vivo as proposed in macrophages. The data in the current study suggest that growth factors secreted by cells in developing atherosclerotic lesions could stimulate scavenger receptor activity in smooth muscle cells and contribute to lipid accumulation and foam cell formation.

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