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Oncostatin M is a mitogen for rabbit vascular smooth muscle cells

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ABSTRACT **The growth regulatory protein oncostatin M was initially discovered in macrophage-conditioned medium. We investigated the effects of oncostatin M on cultured rabbit aorta smooth muscle cells (SMCs) and found that the peptide stimulated an increase in the incorporation of [^{3}H]thymidine into DNA. The magnitude of the stimulation was dependent on oncostatin M concentration and SMC confluency. In subconfluent cultures, 1–2 nM stimulated 4- to 5-fold increases in DNA synthesis after 20 hr. Other structurally related cytokines (granulocyte colony-stimulating factor, leukemia inhibitory factor, interleukin 6, ciliary neurotrophic factor) did not affect SMC DNA synthesis. After 5 or 8 days, oncostatin M caused a doubling in SMC number and also induced a transformed phenotype. The combination of oncostatin M and platelet-derived growth factor for 8 days resulted in a 4-fold increase in cell number, approximately the same increase in cell number as induced by the addition of 10% fetal calf serum. Further investigation suggested that the mitogenic effect of oncostatin M was in part due to tyrosine kinase activation. Within 1–2 min, the factor increased phosphotyrosine levels of several SMC proteins. In addition, detectable increases in diacylglycerol levels occurred within 2–5 min, reached 50% above control by 30 min, and remained elevated through 45 min of incubation with oncostatin M. SMC inositol phosphate levels were also elevated within 2 min and then returned to near control values by 20 min. Within 30 min, oncostatin M induced expression of the immediate-early gene EGR-1. These data indicate that oncostatin M may be an important, naturally occurring mitogen for vascular SMCs.**

Monocyte/macrophages appear to be involved in atherogenesis (reviewed in refs. 1 and 2). They have been reported to adhere to the vessel wall and extravasate at the site of a developing lesion (3–5). Once in the subendothelial space they begin to take up modified lipoproteins and store the lipoprotein cholesterol as cholesteryl esters. In the process they become transformed into foam cells, which are characterized by large fatty vesicles (3). Although the uptake of modified lipoproteins by macrophages is thought to be protective, macrophage/foam cells may also exacerbate the disease process. Recently, Ross and coworkers (6) have shown that human macrophages in vessel wall lesions possess platelet-derived growth factor (PDGF) B protein (6). In addition, it is well accepted that PDGF chemoattracts and mitogenically stimulates vascular smooth muscle cells (SMCs). The recruitment and proliferation of SMCs in the plaque could further stimulate progression of the disease by increasing the size of the atheroma. Although the chemoattractant and mitogenic properties of PDGF for SMCs have been characterized (7, 8), the possible involvement of other macrophage-derived growth factors in atherogenesis has not yet been thoroughly explored.

A growth regulatory protein, oncostatin M, originally found to be secreted by macrophages (9, 10) and T lymphocytes (11), has been reported to share some structural and functional homology with other hematopoietic and neuropoietic cytokines (12, 13). The 28-kDa peptide inhibited the proliferation of some tumor cell lines but also stimulated several normal fibroblast lines to proliferate (9, 14). In addition, the peptide induced the differentiation of some cell types, including stimulation of interleukin 6 production by endothelial cells (15), up-regulation of the low density lipoprotein receptor in liver cells (16), and stimulation of acute-phase proteins and plasminogen activator in liver cells (17). Oncostatin M appears to exert these effects upon binding to a specific cell surface receptor (16, 18) and stimulating increases in the levels of phosphotyrosine proteins as well as other second messenger pathways (16, 19). We investigated the effects of oncostatin M on cultured rabbit aorta SMCs and found that this polypeptide is a potent SMC mitogen.

MATERIALS AND METHODS

Mitogenic Assays. Rabbit thoracic aorta SMCs were from David Hajjar (Cornell) and were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) and penicillin/streptomycin (all from GIBCO). To measure the effect of peptides on proliferation, cells (up to passage 29) were plated sparsely (2×10^4) in six-well Falcon dishes and incubated in medium containing 2% FBS or fresh 10% FBS. Two percent FBS was used because it maintained cultures for 8 days without stimulating large increases in proliferation. Growth factors were added to monolayers in the presence of 2% FBS. Cell number was determined after 5 or 8 days using the fluorescent probe-based Live/Dead assay (Molecular Probes) and a Cytofluor 2300 (Millipore). Alternately, the cells were stained with rose bengal solution [6% in phosphate-buffered saline (PBS)] for 10 min and then washed four times with PBS before solubilizing the cell-associated dye with ethanol (50%). Optical densities were measured with a microtiter plate reader. Occasionally the cells were removed from the dishes by mild trypsinization and counted with a hemocytometer.

DNA Synthesis. SMCs were plated at 1×10^5 per well (12 wells) or at 0.5×10^5 per well (24-well dishes) and allowed to adhere overnight in the presence of 10% FBS. The following day the media were replaced with DMEM and the appropriate growth factor. Twenty hours later the SMCs were pulsed with 1 μCi of [^{3}H]thymidine per ml (25 Ci/mmol; 1 Ci = 37 GBq) for 2 hr. The monolayers were washed twice with PBS and then precipitated with ice-cold trichloroacetic acid (5%) for 20 min. After three additional washes, the precipitates were solubilized with 0.2% sodium dodecyl sulfate (SDS) and assayed for radioactivity in a scintillation counter. PDGF antibodies were from Genzyme.

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Abbreviations: SMC, vascular smooth muscle cell; PDGF, platelet-derived growth factor; FBS, fetal bovine serum.

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Lipid Analysis. Lipids from cells radiolabeled with [^{3}H]-glycerol (50 Ci/mmol) were extracted by the method of Bligh and Dyer (20). Extracts, dried under a stream of nitrogen, were solubilized with 50 μl of chloroform, spotted on thin-layer chromatography plates (Merck), and resolved using a mobile phase consisting of petroleum ether:ethyl acetate, 80:20 (vol/vol). Neutral lipid standards (diacylglycerol and triacylglycerol, Sigma), added to the lipid extracts before chromatography, were identified with iodine vapors and, along with spots at the origin (phospholipids), were scraped into vials. Radioactivity was quantitated with a scintillation counter.

Phosphotyrosine Analysis. SMCs were plated in 100-mm Falcon dishes at 2×10^6 per dish. After 24 hr, the cells were incubated with growth factors and/or inhibitors (genistein was from ICN; orthovanadate was from Sigma), washed once with 4°C PBS, and lysed with 200 μl of SDS sample buffer containing 50 mM 2-mercaptoethanol and 500 μM sodium orthovanadate. The samples were analyzed by Western blotting techniques as described (14).

Inositol Phosphate Analysis. Cells ($\approx 4 \times 10^6$ per 100-mm dish) were preincubated with [^{3}H]inositol (6 hr, 10 μCi/ml), treated with growth factors for various times, and then precipitated with trichloroacetic acid (5%) for 20 min at 4°C. The supernatant fluids were extracted five times with equal volumes of ethyl ether, dried under a stream of nitrogen, and brought up to 300 μl with water. Aliquots were separated by HPLC using a Partisil 10 SAX column (Whatman) by the ammonium phosphate gradient method of Dean and Moyer (21). Radioactivity was monitored on line and peaks of radioactivity were analyzed with a Radiomatic Flo-one detector (Packard).

RNA Isolation and Northern Blot Analysis. The 3.1-kb murine EGR-1 cDNA (kindly provided by V. P. Sukhatme, University of Chicago) was purified from plasmid pUC13 after digestion with *Eco*RI. The human c-*jun* cDNA (2.6 kb) was purified from plasmid vector pGEM2 after digestion with *Eco*RI. The human c-*fos* genomic probe (9 kb) was purified from plasmid vector pBR322 after digestion with *Eco*RI. The human γ-actin cDNA (1.0 kb) and the human c-*myc* genomic probes (exon 3, 1.2 kb) were kindly provided by Jill Lacy (Yale University, New Haven, CT). For mRNA detection, purified inserts were radiolabeled to a specific activity of 10^9 cpm/μg using [^{32}P]dCTP (Amersham) and purified with G-50 Sephadex columns.

SMCs ($\approx 4 \times 10^6$ per 100-mm dish) were preincubated with oncostatin M, washed with PBS, and lysed in guanidinium isothiocyanate. Total RNA was isolated by ultracentrifugation through a cesium chloride cushion, separated by electrophoresis in 1.2% agarose gels (10 μg per lane) containing 6% formaldehyde, stained with ethidium bromide, and transferred to nitrocellulose membranes (22). Prehybridization, hybridization, washing, autoradiography, and densitometry were as described (19). Some blots were stripped and reprobed with γ-actin to verify that equivalent amounts of RNA were being assayed.

RESULTS

Oncostatin M-Stimulated Mitogenesis of SMCs. The ability of oncostatin M to stimulate DNA synthesis in SMCs was investigated. The concentration of oncostatin M required to give a half-maximal response after 20 hr of incubation was approximately 8 ng/ml (Fig. 1*A*). At concentrations of 12 ng/ml (0.4 nM) or higher, the peptide stimulated a maximal increase (4-fold) in [^{3}H]thymidine incorporation (Fig. 1*A*). In comparison, PDGF-BB at 10 ng/ml ($\approx$0.4 nM) increased [^{3}H]thymidine incorporation by 6- to 7-fold (Fig. 1*A*), whereas serum induced a 12-fold stimulation in DNA synthesis (data not shown). Neutralizing antibodies to PDGF

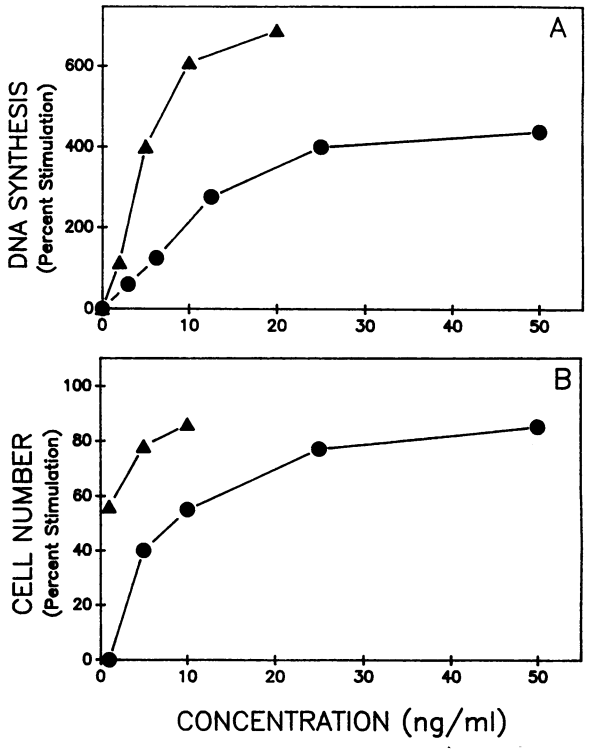

FIG. 1. Stimulation of SMC proliferation by oncostatin M or PDGF. Cells were incubated for either 20 hr (*A*) or 5 days (*B*) with the indicated concentrations of either oncostatin M (●) or PDGF (▲). Cell plating densities were altered (see text) to give 60% confluent monolayers at 20 hr or $\approx$100% confluency at 5 days (for cells incubated in 10% serum).

(either A or B chains) were unable to prevent DNA synthesis stimulated by oncostatin M (data not shown).

Additionally, the effects of oncostatin M on cell number were investigated. After 5 or 8 days of culture, optimal concentrations of oncostatin M or PDGF induced an $\approx$2-fold increase over 2% serum controls, whereas 10% serum induced a 3- to 5-fold increase (Table 1, Fig. 1*B*). Combination of the two growth factors yielded an additional increase over the effects of either peptide alone (Table 1). After 8 days of incubation, oncostatin M plus PDGF gave as great an increase in cell number as 10% serum (Table 1), suggesting that the growth factor combination could replace most of the mitogenic activity in serum. In addition to stimulating proliferation, oncostatin M induced a transformed or spindle-like

Table 1. Stimulation of SMC proliferation by oncostatin M

Addition	Cell no., % of control	
	5 days	8 days
2% serum	33	27
+ oncostatin M	60	53
+ PDGF	62	59
+ oncostatin M and PDGF	79	99
10% serum control	100	100

SMCs were plated in six-well dishes at 2×10^4 in DMEM and 10% FBS to keep initial plating density at <5%. The next day, media were removed and replaced with DMEM containing 2% FBS and 50 ng of recombinant human oncostatin M per ml (44) and/or 10 ng of PDGF per ml or DMEM and 10% FBS. Cell number was determined on the fifth or eighth day. On days 3 and 6, media were replaced. These conditions were designed to yield nearly confluent monolayers by day 5 for cells incubated in the presence of 10% serum. For 10% serum controls, the number of cells was $\approx$225 (5 days, average of four experiments) or $\approx$1500 (8 days, average of two experiments) $\times 10^4$.

morphology that partially resembled the shape of PDGF-treated cells (Fig. 2 *C* and *D*). When the two growth factors were combined, the SMCs appeared to lose contact inhibition and began to overlap (Fig. 2*E*). In contrast, cells in 10% serum exhibited a cobblestone morphology and were clearly contact inhibited (Fig. 2*B*).

Oncostatin M is a member of a family of related cytokines that include leukemia inhibitory factor, interleukin 6, granulocyte colony-stimulating factor, and ciliary neurotrophic factor, as reported by Rose and Bruce (12) and Bazan (13). Although many of the biologic properties of these related factors are unique, certain others are shared by two or more members of the family (12, 13). We decided to test other members of the family for their ability to stimulate the growth of rabbit SMCs. The results shown in Table 2 indicate that none of the other related cytokines was able to affect DNA synthesis.

Effect of Oncostatin M on Tyrosine Phosphorylation. It was recently reported that oncostatin M stimulated tyrosine phosphorylation in liver cells (16). Therefore we investigated the effects of the peptide on SMCs. Oncostatin M induced rapid increases in tyrosine phosphorylation of several proteins. New bands appeared around 150 kDa, at 80 kDa, and at 60 kDa. Additionally, increases in phosphorylation occurred in proteins of 106–130 kDa (Fig. 3*A*). The effects of oncostatin M on tyrosine phosphorylation depended on incubation time. At 50 ng/ml, an increase in phosphorylation of the 150-kDa protein was observed within 2 min and returned to unstimulated values by 45 min (Fig. 3*B*). Protein tyrosine phosphorylation was detectable at concentrations of oncostatin M as low as 5 ng/ml (not shown).

To determine the role of oncostatin M-induced tyrosine phosphorylation in mitogenesis, SMCs were treated with the tyrosine kinase inhibitor (genistein) and a phosphotyrosine phosphatase inhibitor (orthovanadate). Pretreatment of SMCs with genistein (30 μg/ml for 45 min) dramatically decreased oncostatin M-stimulated [^{3}H]thymidine incorporation (Table 3). On the other hand, pretreatment with orthovanadate (30 μM for 30 min) further enhanced the ability of oncostatin M to increase DNA synthesis (Table 3).

Table 2. Specificity of the growth stimulatory effect of oncostatin M on vascular SMCs

Addition	Conc., ng/ml	DNA synthesis, fold stimulation
None		1.0
Oncostatin M	50	4.3
LIF	100	1.1
IL-6	50	1.3
CNTF	50	1.0
GM-CSF	50	1.5
G-CSF	50	1.4

Cells were plated in 24-well dishes in 10% FBS and DMEM. The next day the media were removed and replaced with DMEM with the indicated amounts of oncostatin M, leukemia inhibitory factor (LIF), interleukin 6 (IL-6), ciliary neurotrophic factor (CNTF), granulocyte/monocyte colony-stimulating factor (GM-CSF), or granulocyte colony-stimulating factor (G-CSF). After 20 hr, the monolayers were incubated for 2 hr with [^{3}H]thymidine and incorporation of label into DNA was quantitated. Monolayer confluencies were ≈60% during incubation with [^{3}H]thymidine.

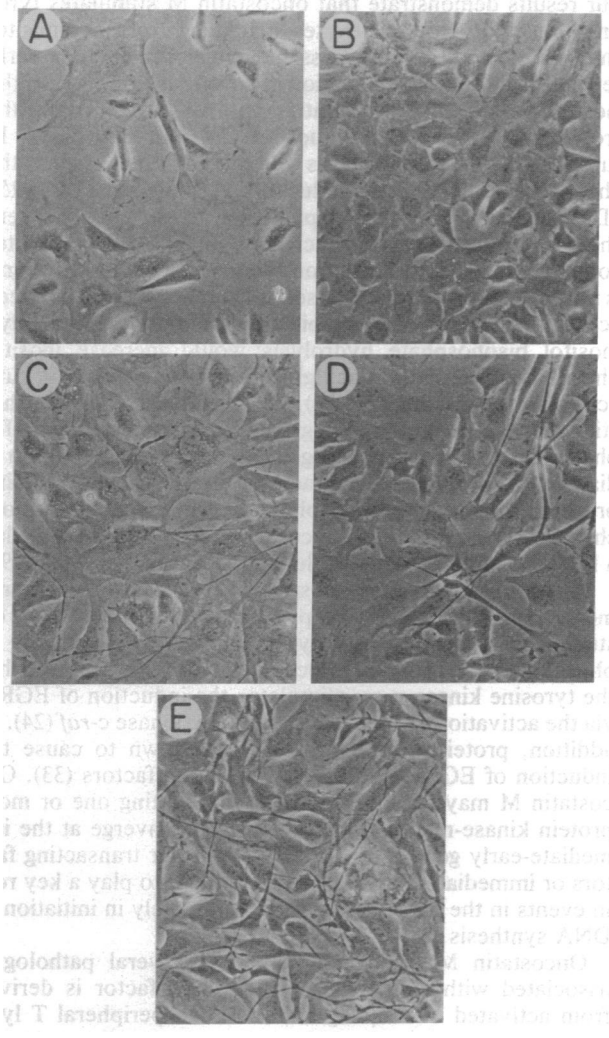

FIG. 2. Oncostatin M increases SMC number and alters morphology. Pictures were taken from the day 5 cultures used in Table 1. (×170.) Cells were incubated for 5 days in 2% serum (*A*), 10% serum (*B*), or 2% serum plus oncostatin M (*C*), PDGF (*D*), or the two growth factors combined (*E*). Each picture is representative of the cell morphology and monolayer confluency of the entire well.

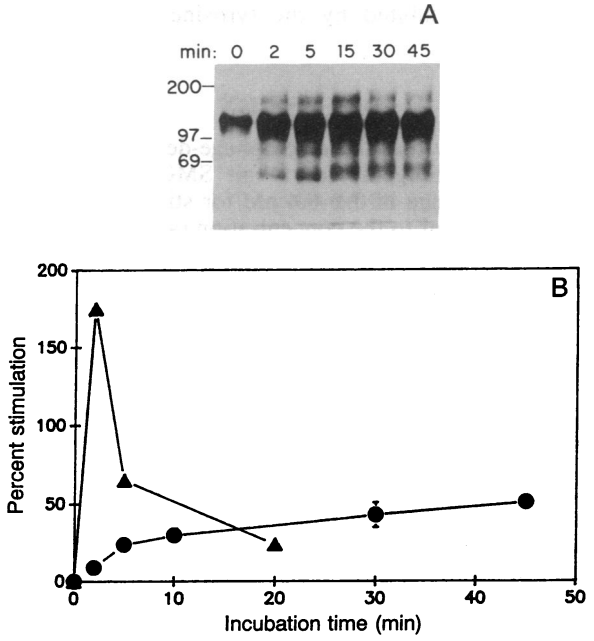

FIG. 3. (*A*) Time dependence of the stimulation of tyrosine phosphorylation by oncostatin M (50 ng/ml). Molecular masses are indicated in kDa. (*B*) Stimulation of diacylglycerol and inositol phosphates by oncostatin M. SMCs (≈60% confluent in 100-mm dishes) were incubated with radiolabeled glycerol or inositol for 6 hr and were stimulated with oncostatin M (100 ng/ml) for the indicated times before analyzing diacylglycerol (●) or inositol phosphates (▲).

Table 3. Role of tyrosine phosphorylation in oncostatin M-stimulated SMC DNA synthesis

Addition	DNA synthesis, cpm per monolayer	% of control
Control	3,324	
Vanadate	5,141	155
Oncostatin M (10 ng/ml)	12,885	388
+ vanadate	18,813	566
Genistein	3,250	98
Oncostatin M (50 ng/ml)	21,000	632
+ genistein	10,000	301

Cells were plated at 2×10^6 per 100-mm dish to achieve 60% confluent monolayers the next day. Genistein (30 μg/ml) or sodium orthovanadate (30 μM) was added for 30–45 min. Oncostatin M (50 ng/ml with genistein or 10 ng/ml with vanadate) was added and 20 hr later the cells were assayed for DNA synthesis.

Stimulation of Diacylglycerol and Inositol Phosphates. It has been reported that phospholipase C-γ1 activity can be induced by a mechanism that involves tyrosine kinase activation (23). Therefore, we investigated the effects of oncostatin M on inositol phospholipid-related second messengers. Within 2–5 min of addition, oncostatin M elevated SMC diacylglycerols. The diacylglycerol levels increased by 50% within 30 min and continued to increase through 45 min of treatment (Fig. 3*B*). However, the time dependence for production of inositol phosphates was markedly different. Increases stimulated by oncostatin M had reached a maximum by 2 min and subsided to near baseline values by 20 min of incubation (Fig. 3*B*).

Immediate-Early Gene Induction. Since activation of tyrosine kinase has been shown recently to stimulate the transcription of EGR-1, an immediate-early gene induced by growth factors (24), we investigated the effect of oncostatin M on EGR-1 message in SMCs. As shown in Fig. 4, oncostatin M caused a strong and transient induction of the EGR-1 gene. EGR-1 mRNA was induced 10-fold by 30 min and returned to control levels by 2 hr. This immediate/early gene response was inhibited by the tyrosine kinase inhibitor genistein (Fig. 4).

DISCUSSION

Our results show that the macrophage-derived peptide oncostatin M is mitogenic for rabbit SMCs. The effective concentration range of 0.1–0.4 nM for stimulation of DNA synthesis is similar to the concentration range of PDGF-BB-mediated mitogenesis in these cells. The maximal stimulation of DNA synthesis induced by 25 ng of oncostatin M per ml after 20 hr was ≈60% of the stimulation induced by 10 ng of PDGF per ml and 30% of the stimulation induced by fresh serum, suggesting that oncostatin M is not as mitogenically effective as PDGF. However, when cell number was measured after 5 or 8 days of incubation, the two growth factors gave similar increases (≈60% of the increase stimulated by serum) at optimal concentrations. In addition, the combination of oncostatin M and PDGF gave cell number increases that were similar to those induced by serum, especially after 8 days of incubation. These results are consistent with the possibility that oncostatin M acts by a unique mechanism and complements the effects of PDGF such that together the two growth factors can replace the proliferative potential of normal serum concentrations in SMC cultures.

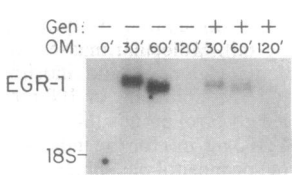

FIG. 4. Oncostatin M induction of EGR-1. SMCs (≈60% confluent in 100-mm dishes) were treated with oncostatin M (OM; 50 ng/ml) or genistein (Gen; 30 μg/ml) for the times shown and then analyzed for immediate-early gene message.

Another interesting finding is that oncostatin M induced an unusual spindle-like morphology, which resembled the morphology of PDGF-treated cells but with distinct differences. Oncostatin M induced longer but thinner pseudopodia compared to PDGF. Furthermore, when the two growth factors were added together, the oncostatin M phenotype appeared to dominate, and the cells lost contact inhibition and began to pile up on each other. This effect became more apparent the longer the cells were maintained in culture in the presence of the two growth factors.

The signal transduction pathways stimulated by oncostatin M appear to have much in common with other growth factors that activate tyrosine kinases. Upon binding PDGF, a tyrosine kinase domain in the cytosolic tail of the PDGF receptor is activated (25). The 180-kDa PDGF receptor rapidly phosphorylates itself as well as several intracellular enzymes, including GTPase activating protein, phospholipase C-γ1, and phosphatidylinositol kinase (3-position) (25–27). After phosphorylation, phospholipase C-γ1 hydrolyzes phosphatidylinositol bisphosphate and generates the intracellular messengers diacylglycerol and inositol trisphosphate (23). Finally, stimulation of immediate-early gene message appears to be important in the mitogenic mechanism of PDGF (28). Our results demonstrate that oncostatin M stimulates tyrosine phosphorylation, elevates diacylglycerol and inositol phosphates, and elevates message levels of immediate-early genes. In addition, the elevation of second messengers in the inositol phospholipid degradation pathway suggests that the growth factor causes activation of phospholipase C-γ1. In support of this possibility is the finding that one of the phosphotyrosine proteins induced by oncostatin M is ≈150 kDa, the same size as phospholipase C-γ1 (23). The very short time course for the increases in inositol phosphates compared to the longer duration of elevation of diacylglycerol is interesting and has been observed in other pathways of cell activation (29). Initially, a rapid stimulation of phosphatidylinositol bisphosphate hydrolysis would increase inositol phosphate levels and diacylglycerol, which would in turn activate protein kinase C (30). Protein kinase C can further stimulate the activities of degradative enzymes specific for phosphatidylcholine, resulting in the sustained production of diacylglycerol from the degradation of phosphatidylcholine or other non-inositol phospholipids (31, 32). This more chronic elevation of diacylglycerol has been suggested to play a key role in longer-term cellular activation processes (29).

The role of tyrosine phosphorylation in the mitogenic mechanism of oncostatin M appears to be important based on studies with inhibitors of tyrosine kinases (genistein) or phosphatases (vanadate). Recently, it has been shown that the tyrosine kinase v-*src* stimulates the induction of EGR-1 via the activation of the serine-threonine kinase c-*raf* (24). In addition, protein kinase C has been shown to cause the induction of EGR-1 and other transacting factors (33). Oncostatin M may induce EGR-1 by stimulating one or more protein kinase-mediated pathways that converge at the immediate-early gene level. EGR-1 and other transacting factors or immediate-early genes are thought to play a key role in events in the nucleus that result ultimately in initiation of DNA synthesis (28).

Oncostatin M may be involved in several pathologies associated with leukocytes. The growth factor is derived from activated macrophages (9, 10) and peripheral T lymphocytes (11), both of which are present in atherosclerotic lesions (2). Macrophages in lesions have been shown to produce PDGF-B (6), which possesses mitogenic (8) and chemoattractant (7) properties for SMCs. The discovery that oncostatin M is produced by leukocytes and is mitogenic for SMCs raises the possibility of the involvement of oncostatin

M in hyperproliferative vascular diseases such as atherogenesis or restenosis disorders arising from angioplasty. Intimal SMCs involved in these diseases appear to be abnormal not only in proliferative characteristics but also in morphology, exhibiting a spindle-shaped or transformed phenotype (34). The effects of oncostatin M plus PDGF on SMC morphology and contact inhibition could help explain how intimal SMCs acquire increased proliferative potential. Furthermore, oncostatin M has been reported to be not only a major mitogen but also an autocrine growth factor in cells derived from acquired immunodeficiency syndrome-associated Kaposi sarcoma lesions (35, 36). The transformed phenotype conferred to Kaposi cells in culture by oncostatin M (36) is similar to the spindle-shaped phenotype induced in SMCs in the present study. Since Kaposi cells have been suggested to originate from a vascular SMC precursor (36), it is intriguing to speculate that Kaposi cells and intimal SMCs have much in common. The findings that T cells infected with virus (human T-lymphotropic virus, type I) have been shown to produce and secrete oncostatin M (35), and that infection with certain viruses causes T-cell lymphomatosis and results in accelerated atherosclerosis in some animal models (for a review, see ref. 37), are intriguing. In humans, at least two types of viruses have been found in cells or tissues from atherosclerotic lesions (38, 39). These observations suggest that oncostatin M secreted by macrophages or T cells in vessel wall lesions could play a role in the progression of atherosclerosis and may help to explain how virus infection accelerates progression of the disease.

Not all SMCs respond to the mitogenic effects of oncostatin M. We have confirmed the finding that DNA synthesis in normal human SMCs is inhibited by oncostatin M (ref. 36; unpublished observations). In addition, two different isolates of rat aorta SMCs (obtained from ATCC) were unaffected by oncostatin M (unpublished observations). These findings are consistent with the concept that SMCs in culture vary widely and perhaps reflect differences observed in medial and intimal SMCs.

Oncostatin M is a member of a family of cytokines and growth factors that share many biologic properties (12, 13). However, the mitogenic effects of oncostatin M on vascular SMCs appear to be unique. Of the peptides with sequence homologies to oncostatin M (leukemia inhibition factor, ciliary neurotrophic factor, granulocyte colony-stimulating factor) (12, 13), only oncostatin M increased SMC DNA synthesis. In addition, oncostatin M has been reported to bind to GP-130, the signal-transducing component of the interleukin 6 receptor complex (40). In rabbit SMCs, IL-6 had no effect on DNA synthesis, suggesting that these cells do not express the second peptide of the IL-6 receptor complex or that the intracellular signal transduced by oncostatin M is different.

Finally, it is likely that multiple growth factors/cytokines expressed by macrophages are involved in processes that lead to SMC involvement in atherosclerosis. Heparin-binding epidermal growth factor (41) and PDGF (6–8) are secreted by macrophages and have been shown to be potent mitogens for SMCs. Other macrophage-derived growth factors and cytokines have been reported to stimulate SMC proliferation (42, 43). Our current results suggest that oncostatin M also may be involved in vascular diseases that are characterized by abnormal, proliferative SMCs in the intima. It might be possible to interfere with the development of the disease by inhibiting either the conversion of SMCs to an abnormal phenotype or their abnormal growth by inhibiting the effects of oncostatin M on SMCs.

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