CC chemokine receptors are important modulators of inflammation. Although CC chemokine receptors have been found predominantly on leukocytes, recent studies have suggested that vascular smooth muscle cells respond to CC chemokines. We now report that human smooth muscle cells express CCR5, a co-receptor for human immunodeficiency virus; CCR5 mRNA was detected by RNA blot hybridization in human aortic and coronary artery smooth muscle cells. The cDNA generated by reverse transcription-polymerase chain reaction from aortic smooth muscle cells had 100% identity throughout the entire coding region with the CCR5 cloned from THP-1 cells. By immunohistochemistry, CCR5 and the CCR5 ligand, macrophage inflammatory protein-1β (MIP-1β), were detected in smooth muscle cells and macrophages of the atherosclerotic plaque. In smooth muscle cell culture, MIP-1β induced a significant increase in intracellular calcium concentrations, which was blocked by an antibody to CCR5. In addition, MIP-1β caused a calcium-dependent increase in tissue factor activity. Tissue factor is the initiator of coagulation and is thought to play a key role in arterial thrombosis. These data suggest that human arterial smooth muscle cells express functional CCR5 receptors and MIP-1β is an agonist for these cells.

Smooth muscle cells (SMCs) are the predominant cellular elements of the arterial media. In the normal arterial wall, SMCs are in a quiescent, contractile state and function primarily to regulate vascular tone. In atherosclerosis, SMCs modulate to a synthetic phenotype, allowing them to proliferate and migrate to form part of the intimal plaque (1). SMC proliferation and hypertrophy are also features of hypertension (2). A variety of growth factors and cytokines found in the atherosclerotic plaque and in the injured arterial wall have been shown to be agonists for SMCs and to modulate their growth and migratory properties (3-5).

CC chemokines are members of a family of highly related proteins characterized by two adjacent cysteine residues (6). These proteins play a crucial role in a variety of inflammatory processes by acting as leukocyte activators and chemoattractants (6, 7). CC chemokines bind to a family of G protein-coupled receptors, CC chemokine receptors (CCRs), characterized by seven transmembrane spanning domains (8). CCRs have been identified predominantly on leukocytes (9, 10). We recently reported that the CC chemokine, monocyte chemotactic protein-1 (MCP-1) specifically binds to human aortic SMCs and induces tissue factor (TF), the initiator of the clotting cascade (11). In these cells, the mRNA encoding the known MCP-1 receptor, CCR2 (12) could not be identified by RNA blot hybridization or by reverse transcription-polymerase chain reaction (RT-PCR). In addition, these cells did not express mRNA for other CCRs, including CCR1 (13), CCR3 (14), CCR4 (15), and DARC (16), as determined by RT-PCR. However, the responsiveness of SMCs to MCP-1 suggested that they expressed a member(s) of the CCR family. Since our initial report, several additional CCRs have been identified (17). In particular, CCR5 has been shown to be the receptor for macrophage inflammatory protein-1 (MIP-1) α and β (18) and to be a co-receptor for macrophage-tropic or dual-tropic strains of human immunodeficiency virus (HIV) (19).

We now report that cultured human arterial SMCs possess CCR5 mRNA and protein. The SMC CCR5 was functionally coupled, responding to MIP-1β with increases in intracellular calcium concentration ([Ca2+]i) and in TF activity. Antibody to CCR5 blocked both the increases in [Ca2+]i and in TF activity. CCR5 and MIP-1β antigens were also detected in SMCs of the atherosclerotic arterial wall. CCR5 and its ligand, MIP-1β, may play a role in mediating the inflammatory and prothrombotic responses associated with atherosclerosis.

EXPERIMENTAL PROCEDURES

Growth Factors and other Reagents—Recombinant human anti-human CCR5 antibody (2D7) and its isotype control antibody were purchased from Pharmingen International (San Diego, CA). Polyclonal anti-human MIP-1β, anti-human CCR5 (monoclonal antibody 182), and anti-human CCR2 antibodies were purchased from R & D Systems (Minneapolis, MN). An inhibitory monoclonal antibody against human tissue factor (20) was the generous gift from Dr. Guha (Mount Sinai School of Medicine, New York, NY). Monoclonal anti-human macrophage CD-68 antibody was purchased from DAKO (Carpinteria, CA). Fetal bovine serum (FBS) was obtained from Sigma Chemical Co. (St. Louis, MO). 3,3′-diaminobenzidine was purchased from Biogenex (San Ramon, CA). Collagenase Type II was purchased from Worthington Biochemical Corp. (Freehold, N. J.). Fura-2/AM was purchased from Molecular Probes (Eugene, OR). BAPTA/AM was purchased from Calbiochem (San Diego, CA). Spectrozyme® factor Xa for
Vascular Smooth Muscle Possess Functional CCR5 Receptors

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Vascular smooth muscle cells (SMCs) are important for the regulation of blood flow. The CCR5 receptor is a G protein-coupled receptor (GPCR) that is expressed in various cell types, including SMCs. To determine whether CCR5 is functional in human SMCs, we used a combination of RNA blot analysis, immunohistochemistry, and calcium imaging. We found that human SMCs express CCR5 and that stimulation with CCR5 ligands leads to an increase in intracellular calcium, indicating the presence of functional CCR5 receptors.

**Cell Culture**—SMCs were isolated from human thoracic aortas and coronary arteries harvested from explanted hearts at the time of cardiac transplantation. Coronary artery SMCs were prepared by enzyme digestion and plated on collagen-coated dishes for 24 h. Primary cultures were prepared by explant (22). Human internal mammary arteries were isolated from patients undergoing coronary artery bypass surgery. SMCs from these specimens were also prepared by explant (23). SMCs were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS, 100 units/ml penicillin, and 100 μg/ml streptomycin and were serially passaged before reaching confluence.

**RNA Preparation and Blot Hybridization**—Extraction of total RNA, agarose gel electrophoresis, transfer to nitrocellulose, and hybridization to 32P-labeled DNA were as described previously (21). Prehybridization and hybridization were performed at 42°C. Final washes for all blots were in 0.1× SSC (1× = 1.0 m NaCl/0.015 m sodium citrate, pH 7.0) and 0.1% SDS at 50°C for 1 h. Hybridization was performed using a 1116-bp segment of the human CCR5 cDNA (bases 584–1699), labeled by random oligomer priming to a specific activity of greater than 108 cpm/mg, and used at 2 × 106 cpm/ml.

**RT-PCR**—RT-PCR was done using the following cycling conditions: for reverse transcription, 5 μg of total RNA was incubated with 0.5 μg of oligoDT12–18 (Life Technologies, Inc., Gaithersburg, MD), at 68°C for 10 min and quick chilled. RNA was then added to reverse transcriptase mix consisting of two hundred units of Superscript II reverse transcriptase (Life Technologies, Inc.), 2.5 mM dNTPs, 1× reverse transcriptase buffer, (Life Technologies, Inc.), 0.1 N dithiothreitol (Sigma). After deparaffinization and hydration with PBS, tissue sections and subsequently exposed to blocking serum for 5 min at room temperature, CCR5 antibody (1 μg/ml), smooth muscle-specific α-actin antibody (0.1 μg/ml), human macrophage-specific CD-68 antibody (7.0 μg/ml), or MIP-1β antibody (1.0 μg/ml) was applied for 2 h at 37°C. Primary antibody was detected as described above. Controls for each experiment included processing the specimens using the nonimmune IgG isotype as the primary antibody and omission of primary antibody. THP-1 cells were used as a positive for CCR5.

**Measurement of [Ca2+]i**—Human SMCs were grown to 60–70% confluence on sterile 25-mm coverslips. Cells were loaded with 10 μM fura-2/AM in 0.1% dimethyl sulfoxide in HEPES-buffered solution containing 145 NaCl mM, 5 KCl mM, 2.5 mM CaCl2, 1.2 mM MgSO4, 11 mM glucose, and 10 mM HEPES for 1 h at 25°C. Measurements of [Ca2+]i were performed as described previously (23, 25–27). Loaded cells were washed three times and placed in a Leiden chamber with 1 ml of HEPES-buffered solution of a Nikko Daphot microscope (Nikon Corp., Melville, NY). All experiments were carried out at 25°C in HEPES-buffered solution. MIP-1β was diluted in 0.2 μl filtered PBS with 0.1% bovine serum albumin (cell-culture grade) and stored at −80°C as per the manufacturer's guidelines. Prior to the addition of agonists, an equal volume of diluent alone was added to cells and recorded for 10 min as a control for possible contamination. Cells that did not respond to MIP-1β were treated with endothelin-1 (10 ng/ml) to establish that they were capable of agonist-mediated [Ca2+]i mobilization. Cells that did not respond to either agonist were excluded from analysis. Cells that responded to endothelin-1 but not MIP-1β were classified as nonresponders. For the blocking experiments, cells were pretreated antibodies or isotype-matched nonimmune IgG for 15 min prior to addition of agonists.

Images were sequentially obtained from a manual gain charge-coupled device camera at excitation wavelengths of 350 and 380 nm by means of a filter wheel (Shutter Instruments, Novato, CA) with emission set at 510 nm by a dichroic mirror. Data were analyzed for [Ca2+]i levels using the Image 1A/FL software package (Media, PA). Pixel by pixel ratio imaging was used to obtain spatial maps. Background light levels were subtracted, and the ratios of the intensities of the individual pixels at the two wavelengths were calculated (operationally logarithmic) were subtracted. Ratio maps were used to obtain spatial maps of [Ca2+]i, in individual SMCs (25, 28). As such, these dual wavelength measurements permitted calculation for [Ca2+]i, in nM, independent of indicator concentration. For these studies, the peak amplitude of the agonist was calculated, and the ratios of the intensities of the individual images obtained at each wavelength were obtained represented the ratio (350:380) of the average of eight images obtained at each wavelength.

**Measurement of Tissue Factor Activity**—Aortic SMCs (passages 3–7) were grown in six-well plates and grown in DMEM with 10% FBS. Prior to treatment, cells were plated DMEM with 0.3% FBS for 24 h. MIP-1β was added to the culture (100 ng/ml) and TF activity was measured as described above. For these studies, the peak amplitude of the agonist activity was calculated using the formula [Ca2+]i = k50 [agonist] (3) (where k50 is the agonist concentration required to produce 50% of the maximal response). For the experiments of Fig. 1B, the second experiment included processing the specimens using the nonimmune IgG isotype as the primary antibody and omission of primary antibody. THP-1 cells were used as a positive for CCR5.

RESULTS

**Identification of CCR5 in Human SMCs**—To determine whether CCR5 is expressed in human SMCs, RNA blot analysis was performed using a 1.1-kb fragment of the human CCR5 cDNA. The CCR5 probe hybridized to a band of a size identical to that found in THP-1 cells (Fig. 1A). No band was seen with RNA from human endothelial cells. To provide further evidence that this band represents CCR5 mRNA, RT-PCR was performed with two different primer pairs. One pair encoded a 300-bp product within the coding region (Fig. 1B); the second encompassed the entire coding region (not shown). Bands of
identical size were seen in lanes containing RNA from SMCs and THP-1 cells. No bands were detected when reverse transcriptase was omitted from the reactions. The SMC bands from aortic SMCs (lanes 1 and 2), THP-1 cells (lanes 3 and 4) and human umbilical vein endothelial cells (lane 4) were hybridized to an 1100-bp fragment of human CCR5. Staining of 18S ribosomal RNA is shown at the bottom. B, RT-PCR. Total RNA from aortic SMCs (lanes 1 and 2) and THP-1 cells (lanes 3 and 4) were amplified using a primer pair specific for a 300-bp fragment derived from the human CCR5 cDNA. In lanes 2 and 4, the reverse transcriptase was omitted.

**Table I**

Calcium mobilization in SMCs in response to MIP-1β

Human internal mammary artery SMCs (IMSMCs), coronary artery SMCs (CASMCs) or aortic SMCs (ASMCs) were loaded with fura-2 and analyzed for [Ca²⁺]i in response to 100 nM MIP1β as described under “Experimental Procedures.” Some cells were treated with 100 nM MIP1β in the presence (+) of a monoclonal antibody (mAb) to CCR5, CCR2, or TF. Total, total number of cells treated. Resp., number of cells showing a 2.5-fold or greater increase in [Ca²⁺]i in response to MIP1β. All values are expressed as the average ± S.E. Time until response was calculated only for responders. Data were pooled from duplicate experiments.

| Cells        | Total | Resp. | Fold response (± S.E.) | Time until response (min) |
|--------------|-------|-------|------------------------|----------------------------|
| IMSMC        | 15    | 11    | 3.7 ± 0.7*             | 4.3 ± 0.8                  |
| + CCR5 mAb  | 9     | 2     | 1.3 ± 0.2*             |                            |
| ASMC         | 10    | 9     | 3.3 ± 0.2*             | 3.3 ± 1.3                  |
| + CCR5 mAb  | 10    | 0     | 1.0 ± 0.1*             |                            |
| + TF mAb    | 8     | 8     | 9.0 ± 3.0*             |                            |
| + CCR2 mAb  | 7     | 6     | 7.5 ± 4.0*             |                            |

*p < 0.05, compared with unstimulated cells.

**Fig. 3.** MIP-1β induces [Ca²⁺]i mobilization. Representative tracings of [Ca²⁺]i, in human aortic SMCs loaded with fura-2. Cells were treated with 100 nM MIP-1β (at the arrow) in the absence (A) and presence (B) of (20 µg/ml) blocking antibody to CCR5.

**MIP-1β to mobilize [Ca²⁺]i, was examined. As shown in Table I and Fig. 3A, MIP-1β induced increases in [Ca²⁺], in internal mammary artery (3.7 ± 0.7-fold), coronary artery (3.3 ± 0.2-fold), and aortic SMCs (10.8 ± 2.6-fold). The average time to a response was 1–4 min and appeared to vary by the anatomic source of the SMCs. As shown in Table I and Fig. 3B, the MIP-1β-induced increase in [Ca²⁺], was blocked by two different antibodies to CCR5, whereas it was not blocked by antibody to the CC chemokine receptor, CCR2. An antibody to TF, an abundant SMC surface molecule not known to mobilize [Ca²⁺], did not block the induction of [Ca²⁺], by MIP-1β. Nonimmune isotype-matched IgG for CCR5 also had no effect on the induction of [Ca²⁺], by MIP-1β (not shown).

**MIP-1β Induces TF Activity in SMCs—Agonist-induced mobilization of [Ca²⁺], has been found to be coupled to gene induction in a variety of cells, including SMCs. TF synthesis, in particular, is mediated via a Ca²⁺-dependent mechanism (21,
To assess the biologic relevance of MIP-1β-induced [Ca\textsuperscript{2+}]i mobilization, we examined the induction of TF activity in aortic SMCs. MIP-1β increased TF activity in a concentration-dependent manner (Fig. 4A). To determine whether the response to MIP-1β (100 ng/ml) was specific for CCR5, the cells were pretreated with a monoclonal antibody to CCR5 (20 μg/ml) (2D7) (Fig. 4B). This antibody significantly reduced the induction of TF activity by MIP-1β, whereas antibody to CCR2 (20 μg/ml) had no effect (Fig. 4B). The nonimmune IgG isotype (20 μg/ml) also had no effect on the induction of TF activity by the MIP-1β (Fig. 4B). To verify that the induction of TF activity by MIP-1β was a consequence of the increase in [Ca\textsuperscript{2+}]i, cells were pretreated with BAPTA/AM (10 μg/ml) to chelate [Ca\textsuperscript{2+}]i prior to addition of MIP-1. This treatment has been shown to block growth factor-mediated increases in [Ca\textsuperscript{2+}]i, and the induction of early genes, including TF, in SMCs (21, 29–31). BAPTA/AM completely blocked the induction of TF activity (Fig. 4C).

**CCRs Expression in the Arterial Wall**—Abundant CCR5 antigen was detected in the fibrous cap, necrotic core, and media of human coronary artery atheroma specimens and localized with α-actin positive SMCs and CD-68 positive macrophages (Figs. 5, A–C). CCR5 was not detected in normal human coronary arteries (Fig. 5C, inset). MIP-1β antigen had a similar distribution in the plaque to CCR5, with antigen detected in the SMCs and macrophages (Fig. 5D). In contrast, CCR2 antigen was detected in the macrophage-rich areas of the plaque (Figs. 5F, green arrows) but not in the α-actin positive regions (Figs. 5F, red arrows). CCR3 antigen had a similar macrophage-restricted pattern of expression (not shown).

**DISCUSSION**

This report describes the presence of functional CCR5 in human vascular SMCs. CCR5 is a member of the family of CCRs and the only known receptor, to date, that binds MIP-1β at physiologic concentrations (7). CCRs have been found largely on leukocytes and have been shown to mediate a variety of biologic processes, including inflammation, chemotaxis, proliferation, and cell activation (6, 32, 33). CCR5 has received particular attention because of its role as a co-receptor for macrophage-tropic strains of HIV (34).

There has been little information about the presence of CCR5 or other CCRs on cells of the arterial wall. CCR5 antigen was identified in blood vessels from a variety of tissues using mono-
Vascular Smooth Muscle Possess Functional CCR5 Receptors

The calcium response and TF induction by MIP-1 receptor, the ability of antibodies to CCR5 to completely block (21, 30, 31). Aged with a contractile response in isolated aortic rings (38–41). Taubman, unpublished observations. Fallon, M. Rossikhina, W. Zhao, G. Christ, J. W. Berman, and M. B. Taubman, unpublished observations.

We recently reported (29) that human aortic SMCs express TF in response to MCP-1. Although high affinity MCP-1 binding sites were identified, RT-PCR failed to demonstrate mRNA for the MCP-1 receptor, CCR2, or for CCR1, CCR3, CCR4, and DARC in cells grown in 10% serum. In a study also employing RT-PCR (37), mRNAs for CCR1 and CCR2 were expressed by human saphenous vein SMCs incubated in serum-free medium for 24 h. CCR3, CCR4, CCR5, CXCR1, and CXCR2 mRNA were not identified in these cells. The detection of CCR5 in our study may be due to differences in study conditions. The former study (37) utilized saphenous vein SMCs, whereas the present study used only arterial SMCs. There were also differences in the culture conditions. Our mRNA was isolated from cells grown in serum-free medium. Our data demonstrate that in addition to possessing CCR5 mRNA, human SMCs contain significant amounts of CCR5 antigen. Most importantly, CCR5 appears to be functionally active, in that these cells respond to MIP-1, the ligand specific for CCR5. Although it is possible that MIP-1β could be acting through a different CC chemokine receptor, the ability of antibodies to CCR5 to completely block the calcium response and TF induction by MIP-1β strongly argues that CCR5 is responsible.

MIP-1α and β are small heparin-binding proteins that are produced by a variety of cells, including macrophages, neutrophils, fibroblasts, and epithelial cells (13). MIP-1α and β are chemotactic agents and activators of monocytes and lymphocytes and, as such, exhibit potent proinflammatory properties. To our knowledge, this is the first report showing that SMCs respond to MIP-1β. MIP-1β caused increases in [Ca2+]i in SMCs derived from aorta, coronary, and internal mammary arteries. The magnitude and time to induction (1–4 min) are similar to those shown for the response of SMCs to platelet-derived growth factor and epidermal growth factor (38–41)2 but distinct from the more rapid (15 s) and pronounced response to the potent vasconstrictor, angiotensin II (42). These growth factor-mediated changes in [Ca2+]i have been associated with a contractile response in isolated aortic rings (38–41) and with the induction of early response genes in SMC culture (21, 30, 31).

MIP-1β treatment resulted in a marked increase in TF activity in human SMCs. This increase was blocked by antibody to CCR5 and by BAPTA/AM, suggesting that its induction was due to CCR5-mediated [Ca2+]i mobilization. TF is considered a key mediator of thrombosis in the setting of atherosclerotic plaque rupture (43–45) and acute arterial injury (46, 47). Of note, the 6-fold induction of TF by MIP-1β is more potent than the induction previously reported in these cells in response to MCP-1 (29) or platelet-derived growth factor (21).

CCR5 acts as a co-receptor for HIV-1 (48). Several experimental animal models of HIV are associated with vascular abnormalities. Transgenic mice carrying a replication-defective HIV-1 provirus with expression restricted to SMCs were shown to develop severe vasculopathy, characterized by intimal thickening, significant luminal narrowing, and thrombotic occlusion (49). A severe arteriopathy, also characterized by intimal thickening, luminal narrowing, and thrombosis, was seen in macaques infected with simian immunodeficiency virus (SIV) (50).

To our knowledge, there have been no reports of direct SMC infection by HIV. The expression of functional CCR5 on SMCs suggests that the question of their infectability should be reexamined. SMCs do not express CD4; however, data using SIV indicate that many primary strains use CCR5 in the absence of CD4. For example, simian microvascular brain endothelial cells that express CCR5 but lack CD4 can be infected with neurotropic SIV strains. This infection can be blocked using CCR5 ligands (51). There is also evidence that soluble CD4, through its binding to GP120, induces conformational changes that facilitate SIV binding and infection via CCR5 (52–55). Thus, it is possible that CD4-independent, CCR5-dependent strains of HIV can be generated that would have the potential to infect SMCs. SMCs could play a role in HIV infection without actually incorporating virus. Infected cells within the vessel wall may elaborate MIP-1β that would then activate SMCs. This could contribute to the arteriopathies reported in patients with AIDS and Kaposi’s sarcoma (56).

MIP-1 antigens and/or mRNAs have been identified at various sites of inflammation (57–59). However, there is limited information regarding their presence in atherosclerotic plaques. By in situ hybridization, low levels of MIP-1 mRNA were found in human carotid endarterectomy samples (3). Our study suggests that MIP-1β antigen is abundant in SMC-rich areas of the plaque. Significantly, intimal and medial SMCs also possess the CCR5 receptor and therefore appear to be competent to respond in vivo to MIP-1β. This report thus raises the possibility that MIP-1β plays a role in the inflammatory and prothrombotic response of SMCs in atherosclerosis.

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