The 24-kDa form of basic fibroblast growth factor inhibits the migration of endothelial cells and mammary carcinoma cells while continuing to promote cell proliferation. This molecule consists of the 18-kDa fibroblast growth factor sequence plus an additional 55 amino acids at the amino-terminal end. Antibody neutralization studies suggested that the inhibition of migration is associated with these 55 amino acids, whereas the promotion of proliferation localizes to the 18-kDa domain. To determine whether 24kD basic fibroblast growth factor could be modified to eliminate its effect on cell proliferation but retain its inhibition of migration, portions of the carboxy-terminal end of 24kD fibroblast growth factor were deleted, and the products were tested on MCF-7 and endothelial cells. A protein consisting of the 55 amino acids of the amino-terminal end and the first 31 amino acids of 18kD basic fibroblast growth factor (ATE31) inhibited migration by 80% but did not promote cell growth. Arginine to alanine substitutions within the first 21 amino acids of the carboxy-terminal end substantially reduced the efficacy of ATE31, whereas substitutions in the remaining part of the molecule had no effect. Competition binding experiments showed that ATE31 does not compete with 24kD basic fibroblast growth factor for binding to fibroblast growth factor receptor 1. In an in vivo matrigel plug assay, 150 nM ATE31 peptide reduced angiogenesis by 80%. These studies demonstrate that the amino-terminal end of 24kD basic fibroblast growth factor is responsible for an activity that inhibits the migration rates of cultured cells as well as the angiogenic response in vivo.

Basic fibroblast growth factor (FGF-2) is a mitogen produced and secreted by endothelial cells, which promotes cell proliferation, chemotaxis, protease production, and integrin expression (1–4). As a consequence, it is an integral component of the angiogenic process. FGF-2 is mitogenic for a number of cells of different types including endothelial cells, fibroblasts (3T3 cells), and mammary carcinoma cells (MCF-7) (5, 6). It has been implicated in cell proliferation and migration during development, wound healing, and tumor growth, and it inhibits apoptosis of endothelial cells (1, 7–12). A single copy gene for FGF-2 encodes for multiple forms of the protein of 24, 22.5, 22, and 18 kDa with the three higher molecular weight isoforms produced by initiation of translation at three CUG codons located upstream from the classical AUG initiation site (13, 14). 24kD FGF-2 consists of the 18-kDa isoform plus an additional 55 amino acids at the amino-terminal end (ATE).

In a recent publication, we demonstrated that endothelial cells could be stimulated to secrete the high molecular weight FGF-2 forms in a regulated manner and to levels capable of affecting cell behavior (5). The effects were 2-fold; these were stimulation of cell proliferation and inhibition of migration. The increase in proliferation was comparable with that promoted by 18kD FGF-2, indicating that the stimulation was independent of the additional amino-terminal peptide. On the other hand, the effect on migration was opposite to that of 18kD FGF-2. Although 18kD FGF-2 promotes cell motility, high-molecular-weight FGF-2 inhibited migration of endothelial cells by 50% and mammary carcinoma cells MCF-7 cells by greater than 70%, even in the presence of unrelated mitogens such as vascular endothelial growth factor and IGF-1 that promote cell migration. Using antibodies specific to the ATE or antibodies to the 18-kDa regions of 24kD FGF-2, we localized the inhibition of migration to the ATE and stimulation of growth to the 18-kDa domain of 24kD FGF-2. Thus, it was concluded that 24kD FGF-2 affects cell behavior differently than 18kD FGF-2 and that the ATE region is responsible for this difference.

To determine whether the growth-promoting activity of 24kD FGF-2 can be separated from its migration inhibitory activity, we synthesized a series of truncated forms of 24kD FGF-2 and tested the ability to promote cell proliferation and inhibition of migration. Results demonstrate that the stimulation of growth of MCF-7 cells is lost with the removal of 40 amino acids from the carboxy-terminal end, while full inhibitory activity is retained. The smallest peptide generated that displayed maximal inhibition contained the amino-terminal 55 amino acids plus the first 31 amino acids of the 18-kDa FGF-2 domain. Despite a requirement for the additional 31 amino acids of 18kD FGF-2, inhibitory activity could be eliminated by replacing specific arginines within the amino-terminal regions with alanines. Thus, as predicted by our antibody experiments, inhibition of migration is a function of the amino-terminal end of 24kD FGF-2.

**EXPERIMENTAL PROCEDURES**

**Construction and Expression of 24kD FGF-2 and Its Mutated Forms** To generate pure recombinant 24kD FGF-2, full-length 24kD FGF-2 cDNA was inserted in-frame into a pPIC9K yeast expression vector (Invitrogen) between the SnaBI and AvrII restriction sites of the pPIC9K vector directly downstream from the DNA encoding the X-factor secretion signal region. The His6 mutant of *Pichia pastoris* GS115, the methanol utilization-positive phenotype (Mut+), was transformed...
by electroporation with the pPIC9K construct vector linearized with SacI. The His+ yeast transformants were grown on MD plates, and those carrying the kanT gene further selected for multiple integrated copies by replating on plates containing 4.0 mg/ml G418 antibiotic. The multicopy transformant was grown in 50 ml of buffered minimal glycerol medium with glycerol as the sole carbon source until the cultures reached an OD660 of 2–6 (16–16 h). The cells were collected by centrifugation at 1500–3000 × g for 5 min at room temperature, and the cell pellet was resuspended in buffered minimal methanol complex medium to induce expression. The cells were grown for 4 days, and 100% methanol was added every 24 h to a final concentration of 2% to maintain protein expression. The medium was cleared of the yeast by filtration and mixed with 5 ml of heparin-Sepharose for 2 h at 4 °C. The gel was washed with 50 ml of buffer A (20 mM Tris–HCl, pH 7.4, 5 mM EDTA, 2 mM EGTA) and then with buffer A containing 0.5 M NaCl. The recombinant 24kD FGF-2 was eluted with buffer A containing 3 M NaCl. The eluate was dialyzed against 4 liters of 20 mM Tris (pH 7.4), 145 mM NaCl. Protein purity was assessed by 10% SDS-PAGE followed by Coomassie Blue staining and Western blot analysis using antibodies generated against a carboxyl-terminal peptide found within the amino-terminal domain of 24kD FGF-2 (5).

Truncated forms of 24kD FGF-2 were prepared by inserting SfiI restriction sites at the 5′-end of 24kD FGF-2 cDNA and the 3′-end of the sequence generating the required truncation. The cDNA fragment was amplified by PCR and inserted into a modified pET15b vector carrying restriction sites at the 5′-end of the 24kD FGF-2 cDNA and the 3′-end of 24kD FGF-2 is in italics). The 3′-primers for each form were: ATE only, 3′-ATATATGCCCCCGTCGCTCCTGGG-CCCCGCC-5′; ATE+10, 3′-ATATATGGCCCCCGTCGCTCCTGGG-CCCCGCC-5′; ATE+20, 3′-ATATATGGCCCCCGTCGCTCCTGGG-CCCCGCC-5′; ATE+31, 3′-ATATATGGCCCCCGTCGCTCCTGGG-CCCCGCC-5′; ATE+37, 3′-ATATATGGCCCCCGTCGCTCCTGGG-CCCCGCC-5′. The amplified fragments were cut with SfiI and ligated to the vector. The plasmids were used to transform BL-21-CodonPlus (DE-3)-RP competent cells. The cells were cultured in LB medium, and 0.4 mM isopropyl-β-D-thiogalactopyranoside was added for 4 h at 30 °C. When the OD660 value of the culture reached 0.6–0.8 the cells were harvested and suspended in 50 mM phosphate-buffered saline, pH 8.0, 10% glycerol, 300 mM NaCl, 5 mM 2-mercaptoethanol (buffer B). The cells were lysed five times by freeze-thaw, and the particulate matter was removed by centrifugation and filtration through a 0.45-μm syringe filter. The filtrate was added to 5 ml of nickel-nitrirotiacetic acid-agarose, and the mixture was shaken for 2 h at 4 °C. The resin was packed into a column and washed with buffer B containing 10 mM Imidazole and then 50 mM NaCl. The ampicillin was eluted with 400 mM imidazole, and protein was eluted with buffer containing 400 mM imidazole. The protein was dialyzed into 50 mM sodium phosphate, pH 7.6, and analyzed by SDS-PAGE followed by staining and Western blot. Site-specific mutagenesis consisting of arginine to alanine substitutions were performed by PCR using the method of overlap-extension reaction (15). The ATE fragment of ATE+31 was divided into four regions containing 5–4 arginines each, and each region mutated separately (see Fig. 3). The primers employed for each region were: region 1 (R4, 6, 8A), 5′-GAGCCAGGGGCAACGCTGGCCGGCGGGAG-3′; region 2 (R14, 18, 20, 22A), 5′-GGTGGCCTGTCGCTGGCTGG-3′; region 3 (R26, 30, 32, 34A), 5′-GTCGCTGCCGCTGCTGGCCGCTGG-3′; and region 4 (R40, 46, 49A), 5′-GGTGATCCGAGGCCGCTGAGGGCGCGCCGCTGC-3′ (mutations are shown in bold). To produce the mutations in regions 1 and 2 or 3 and 4 the same procedures were used except that one of the mutated forms was used as the target DNA.

Culture of MCF-7 Cells and Migration and Growth Assays—MCF-7 cells were maintained in minimal essential medium supplemented with 1 mM sodium pyruvate, 10% fetal calf serum, and 10 μM insulin at 37 °C under 5% CO2, non-migratory cells on the upper membrane surface were removed with a cotton swab, and the cells that traversed and spread on the lower surface of the filter were fixed and stained with Diff-Quik (Dade-Behring). The filter was mounted on a glass slide, and four phase-contrast photomicrographs per membrane were taken at a magnification of ×100. The number of cells per field was counted from contact sheets, and the results compared with control chambers, which had no 24kD FGF-2 added.

To measure growth rates MCF-7 cells (6 × 103) were plated in growth medium for 48 h, the medium was changed to assay medium containing phenol red-free modified Eagle’s medium supplemented with 1 mM sodium pyruvate and 0.3% lactalbumin hydrolysate plus or minus growth factors, and the cultures were allowed to incubate an additional 24 h. Two hours prior to the termination of the experiment [3H]thymidine was added. The cultures were washed with phosphate-buffered saline and then ice cold methanol (2×), 5% trichloroacetic acid was added twice for 10 min each, and the DNA was extracted with 0.3 N NaOH. The number of cpm incorporated was determined by liquid scintillation.

**Competition Binding Assays—Recombinant 24kD FGF-2 was labeled with 125I using immobilized lactoperoxidase/glucose oxidase (Enzymobeads, Bio-Rad). The specific activity of 125I-24kD FGF-2 was 1 × 106 cpm/μg as determined by trichloroacetic acid precipitation. Labeled protein was separated from free iodine by heparin-Sepharose chromatography using 2 mM NaCl to elute the protein from the column. Binding assays were performed with NIH 3T3 cells plated at 50% confluence on 24-well tissue culture dishes and allowed to grow for 48 h. Prior to the addition of labeled protein, cultures were washed with sodium acetate (pH 4.0), 2 mM NaCl for 1 min to remove bound FGF-2 from both low and high affinity receptors and then rinsed with binding buffer (Dubelco’s modified Eagle’s medium, 0.2% bovine serum albumin, 25 mM Hepes, pH 7.3). 125I-24kD FGF-2 (2 ng) was added with various concentrations of unlabeled ligand (0–200 ng) in a final volume of 0.5 ml, and the cells were incubated for 2 h at 4 °C. The cells were washed twice with cold phosphate-buffered saline and lysed with 0.1 N NaOH, 1% SDS, and the radioactivity in the lysates was measured by γ-counting.
Immunoblot Analysis—Cells were washed twice in Dulbecco’s phosphate-buffered saline and then lysed with 0.5% Triton X-100 in 10 mM imidazole (pH 7.15), 40 mM KCl, 10 mM EGTA, 1 mM phenylmethylsulfonyl fluoride, 100 mM benzamidine, and 100 μM leupeptin. The lysates were centrifuged for 2 min at 14,000 g to pellet cell debris and then subjected to the BCA protein assay (Pierce). The Triton X-100-insoluble material remaining on the flask, containing the cell nuclei, was washed twice with the lysis buffer and then solubilized in SDS-PAGE-reducing sample buffer (50 mM Tris, pH 6.8, 5% β-mercaptoethanol, 2% SDS, and 10% glycerol). Samples representing equivalent amounts of each fraction were subjected to electrophoresis on 12% polyacrylamide gels. Upon completion of electrophoresis, proteins were transferred to nitrocellulose membranes, blocked for 1 h at room temperature in 5% nonfat milk in 20 mM Tris, pH 7.4, 145 mM NaCl with 0.05% Tween 20 (TTBS), and then incubated with dilutions of primary antibodies in TTBS containing 0.1% bovine serum albumin. Antibodies used were: anti-18kD FGF-2 monoclonal antibody (Sigma) or a polyclonal antibody made against a 12-amino acid fragment within the amino-terminal end of 24kD FGF-2 (5), anti-ERK, anti-phospho ERK, anti-AKT, or anti-phospho AKT (Upstate Biotechnology). Bound antibody was detected using donkey anti-mouse or rabbit IgG conjugated to horseradish peroxidase (Jackson Laboratories) and the ECL chemiluminescence reagent (Pierce).

In Vivo Assessment of Angiogenesis and Tumor Growth Using the Matrigel Plug Assay—Ice-cold matrigel (500 μl) (Collaborative Biomedical Products, Inc., Bedford, MA) was mixed with heparin (50 μg/ml), FGF-2 (400 ng/ml), and ATE+31 as indicated. The matrigel mixture was injected subcutaneously into 4–8-week-old female athymic Ncr nude mice at sites near the abdominal midline with three injections per mouse. Injection sites were chosen such that each animal received a positive control plug (FGF-2 and heparin), a negative control plug (heparin plus buffer), and a plug containing the treatment to be tested (FGF-2, heparin, and ATE+31). All treatments were tested in triplicate. Animals were sacrificed by cervical dislocation 5 days after injection. The mouse skin was detached along the abdominal midline, and the matrigel plugs were recovered and scanned immediately at high resolution. Plugs were then dispersed in water and incubated at 37 °C overnight. Hemoglobin levels were determined using Drabkin’s solution (Sigma) according to the manufacturer’s instructions. In vivo assessment of the effect of ATE+31 on tumor growth was performed by incorporating two million MatLyLu prostate carcinoma cells into 0.5 ml of matrigel in the presence or absence of 400 ng ATE+31, and the gels were placed subcutaneously into 4–8-week-old female athymic Ncr nude mice at sites near the abdominal midline. After 7 days the gels were removed, photographed, and weighed.

RESULTS

Truncated forms of 24kD FGF-2 were generated by deletion mutagenesis through the placement of stop codons within 24kD FGF-2 cDNA. Initially, two forms were produced containing deletions of one or both putative receptor binding sites (ATE+31, which excludes the carboxyl-terminal binding site and ATE+31, which lacks both binding sites) (Fig. 1). To determine the effect of these truncations on the growth-promoting activity of 24kD FGF-2, the ATE+31 and ATE+31 peptides were added to MCF-7 cells, and the rate of cell proliferation, as determined by thymidine incorporation, was compared with 18kD FGF-2 (8–10-fold). How-
however, no stimulation of proliferation was observed with either of the truncated forms of 24kD FGF-2 at concentrations equal to those used for 24- or 18kD FGF-2 (Fig. 2). Increasing the concentration of ATE+31 to $1 \times 10^{-9}$ did not promote proliferation. Thus, the growth stimulatory effect of 24kD FGF-2 is dependent on the presence of the carboxyl-terminal portion of 24kD FGF-2. However, this was not the case with the inhibition of migration. Employing the Boyden chamber assays with IGF-1 as a chemoattractant, we observed a decrease in MCF-7 cell migration of 64.5% with 24kD FGF-2 at concentrations equal to those used for 24- or 18kD FGF-2 (Fig. 2). However, this was not the case with the inhibition of migration. Employing the Boyden chamber assays with IGF-1 as a chemoattractant, we observed a decrease in MCF-7 cell migration of 64.5% with 24kD FGF-2 and increasing concentrations of unlabeled 24kD FGF-2 or ATE+31. Values shown are the means of triplicate samples ± S.D. and are representative of three or more experiments. The results presented as a percent of maximal 24kD FGF-2 binding in the absence of competitor.

Further attempts to determine whether the inhibitory activity was dependent on specific regions within the ATE involved arginine to alanine substitution. Because of the large number of arginines in the ATE, the sequence was separated into 4 regions each containing 3 or 4 arginines (Fig. 3). Each region was modified separately, and the effect on inhibition of migration was tested and compared with the unmodified ATE+31. Conversion of arginine to alanine in the two regions at the carboxyl-terminal end of the ATE (3 and 4) had little effect on the migration rates; these molecules still inhibited migration by 70–75%. However, arginine to alanine substitutions within either of the two regions at the amino-terminal end (1 and 2) reduced the inhibitory activity of ATE+31; cell migration was 50% of untreated cultures as opposed to 20% for the wild-type ATE+31. The inhibition of migration could be reduced even further by combining regions 1 and 2, resulting in less than 15% inhibition of migration.

The localization of the inhibitory activity to the amino-terminal end of 24kD FGF-2 suggests that there is some interaction between this portion of the protein and the cells that it is affecting. In previous studies, it was shown that the FGF receptor to which 24kD FGF-2 binds in endothelial, MCF-7, and 3T3 cells is FGFR1 (16). To determine whether ATE+31 contains a major binding domain for interaction with FGFR1, competition binding experiments were performed with iodinated 24kD FGF-2 versus unlabeled 24kD FGF-2, 18kD FGF-2, or ATE+31 (Fig. 4). Competition between labeled 24kD FGF-2 and itself resulted in a dose-dependent decline in the binding of labeled protein with an 81 ± 3% decrease in binding at a 100-fold excess. At this concentration, 18kD FGF-2 also caused a similar reduction in the binding of 24kD FGF-2 (79 ± 5%). However, ATE+31 had no significant effect on the binding of $^{125}$I-24kD FGF-2 even at a 1000-fold excess, suggesting that no major FGFR1 binding sites are found within the amino-terminal portion of 24kD FGF-2. To determine whether ATE+31 had the ability to activate an FGFR1-regulated signaling pathway, its effect on ERK1/2 activation was analyzed using phosphospecific antibodies (Fig. 5). In both MCF-7 cells and endothelial cells 24kD FGF-2, at a concentration of $4 \times 10^{-11}$ M, stimulated the phosphorylation of ERK1/2, a response that also occurs in 3T3 cells (16). However, at the same molar concentration...
ATE+31 failed to affect ERK1/2 phosphorylation in these cells. Increasing the concentration to $4 \times 10^{-11}$ M had no effect on the level of ERK phosphorylation.

The effect of ATE+31 on angiogenesis was tested directly by implanting matrigel plugs impregnated with vehicle, $4 \times 10^{-11}$ M 18kD FGF-2, and 18kD FGF-2 plus 15 or 150 nM ATE+31 into mice and measuring the degree of vascular formation. In the presence of FGF-2 alone, there was a robust angiogenic response indicated by the pink hue distributed throughout the presence of FGF-2 alone, there was a robust angiogenic re-

FIG. 6. In vivo assessment of the effect of ATE+31 on angiogenesis. A, female athymic Ncr nude mice were injected subcutaneously at three sites near the abdominal midline with matrigel (500 μl) mixed with heparin (25 μg), FGF-2 (20 nm), and ATE+31 as indicated. Injection sites were chosen such that each animal received a positive control plug (FGF-2 and heparin), a negative control plug (heparin plus buffer), and a plug containing the treatment to be tested (FGF-2, heparin, and ATE+31). All treatments were tested in triplicate. B, quantitative analysis of neovascular development in matrigel plugs in vivo. Matrigel plugs were excised from the animals, dispersed in water, and incubated at 37°C overnight. Hemoglobin levels were determined using Drabkin’s solution (Sigma) according to the manufacturer’s instructions. The results were quantitated spectrophotometrically at 540 nm and are presented as a percentage of the amount of hemoglobin present in plugs not containing added growth factor (left panel). The basal level of angiogenesis occurring in the absence of 18kD FGF-2 was subtracted from the hemoglobin levels in the treated plugs, and the results were presented as a percentage of that occurring in the presence of 18kD FGF-2 alone (100%, right panel).

The addition of 24kD FGF-2 to endothelial cells and MCF-7 breast carcinoma cell has two effects, stimulation of cell proliferation and inhibition of migration (17). Using antibodies pre-
pared against the 18-kDa FGF-2 region or the amino-terminal end of 24kD FGF-2, these two activities were localized to different regions of the molecule (5). Antibodies to 18kD FGF-2 blocked the proliferative activity of 24kD FGF-2 but had no effect on the inhibition of migration, whereas an antibody made against a 12-amino acid peptide within the amino-terminal end of 24kD FGF-2 (and not present in 18kD FGF-2) blocked the inhibition of migration but not proliferation. Thus, we concluded that inhibition of migration was a function of the amino-terminal 55 amino acids present in the larger molecule (5). To identify additional portions of 24kD FGF-2 that were necessary for full activity, the full-length protein was truncated at several sites, and the shorter forms were tested for proliferative and inhibitory activity. A protein containing the ATE plus the amino-terminal 77 amino acids of 18kD FGF-2 retained full migration inhibitory activity but had lost all of the growth-promoting activity. Maximal inhibitory activity was still retained following the removal of 80% of the 18-kDa region of 24kD FGF-2, leaving the ATE plus the first 31 amino acids. These 31 amino acids were critical for the inhibitory activity because reducing the molecule to the ATE plus 20 amino acids diminished the inhibition of migration. It is also apparent from these studies that specific regions within the 55-amino acid amino-terminal end are critical for the inhibitory activity. Results from the arginine to alanine substitution studies show that inhibition of migration requires the extreme amino-terminal end of the molecule (first 22 amino acids) to be intact, whereas altering the remaining portion of the 55 amino acids in the same manner has no effect. Thus, there is a specific requirement for both ends of the ATE+31 for complete inhibition of migration. Although modifying the intervening sequence does not have an effect on the inhibition, this region may be important for maintaining the proper orientation of the molecule.

The lack of competition between the full-length and truncated forms of 24kD FGF-2 in the binding experiments indicates that the truncated protein does not contain a site that can interfere with the binding of full-length 24kD FGF-2 to its receptor. This is not surprising since the defined receptor binding regions of 18kD FGF-2, which competes successfully with 24kD FGF-2 for binding, lie outside the area encompassed by the ATE+31 (Fig. 1). Furthermore, because the inhibition of migration by ATE+31 occurs in the presence of three unrelated growth factors, it is very likely that ATE+31 affects the cells through a point downstream of the ligand-receptor interaction.

One possible site of interaction is the reversal of ERK-dependent cPLA2 phosphorylation, which has been shown to promote endothelial cell migration (18). However, our data (Fig. 5) indicate that ATE+31 has no effect on the constitutive levels of ERK phosphorylation and that 24kD FGF-2 stimulates ERK phosphorylation in the same manner as 18kD FGF-2 (16).

Regardless of the mechanism of action of ATE+31, the results from the animal studies clearly show that the inhibition of migration observed in vitro is associated with a reduction in the rate of angiogenesis in vivo. Instead of the >3-fold increase in blood vessel formation seen with 22 nM 18kD FGF-2 alone, the presence of 150 nM ATE+31 reduces this increase to little more than what occurs in the absence of any added growth factor. By subtracting the basal rate of angiogenesis in the absence of 18kD FGF-2 from that occurring with ATE+31 and FGF-2, it is evident that ATE+31 blocks the FGF-2-induced angiogenic response almost completely. Even at 15 nM there is an obvious reduction in vascular formation. Thus, these results indicate that inhibition of endothelial cell migration is sufficient to block angiogenesis in vivo, even when cell proliferation is unaffected.

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Inhibition of Cell Migration and Angiogenesis by the Amino-terminal Fragment of 24kD Basic Fibroblast Growth Factor
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