Here we describe the cloning of the regulator of fibroblast growth factor 2 (FGF-2) transcription (RFT) using a yeast one-hybrid screening with a defined motif in FGF-2 promoter as a target sequence. Overexpression of human RFT (RFT-A) reduces FGF-2 RNA and protein levels in both normal and tumor cell lines. Its splice variants, RFT-A' and RFT-B, have deletions in the putative DNA binding domain and fail to bind FGF-2 promoter and repress FGF-2 gene expression. The ratios of RFT isoforms differ between normal and tumor cells, with the splice variants dominating in tumor cells. Overexpression of RFT-A induces glioma cell death. Our data suggest that regulation of FGF-2 by RFT is important for cellular functions and may be impaired in certain tumors.

Fibroblast growth factor 2 (FGF-2) is a mitogen for neuroectoderm- and mesoderm-derived cells (1) as well as a potent angiogenic factor in vivo (2). FGF-2 acts in an autocrine or a paracrine manner, interacting with its specific receptors (3), and has been shown to play an important role in limb bud formation (4) and neural tissue formation (5). In addition, a role for FGF-2 has been suggested for brain diseases such as tumors (5–7), Alzheimer’s disease (8), and Huntington’s disease (9). Ninety percent of gliomas overexpress FGF-2 constitutively, and FGF-2 may play a crucial role in tumorigenesis and tumor progression of gliomas by acting through an autocrine mechanism (5–7). Although a clear case has been made for the involvement of FGF-2 in development and diseases, little is known about the regulation of FGF-2 gene expression at the transcriptional level (10–15). Many factors have been shown to stimulate FGF-2 expression. In adrenal chromaffin cells, stimulation of acetylcholine nicotinic receptors, or angiotensin II receptors, or direct stimulation of adenylate cyclase (with forskolin) or protein kinase C (with phorbol ester) increases the level of all FGF-2 isoforms (13). In primary astrocytes, endothelin-3 increases and natriuretic peptide decreases FGF-2 expression through modulating immediate early gene, egr-1 (10). FGF-2 has also been shown to function in both paracrine and autocrine manners, such that positive feedback may be the basis for neoplastic transformation (16).

FGF-2 promoter contains no TATA box but has multiple GC-rich regions for transcriptional initiation. The promoter contains putative sites for several transcription factors such as Sp1 and Egr-1 (10, 15). The homeodomain protein, HOXD7, was shown to bind a +130 to +159 sequence and increase FGF-2 expression (11), and Egr-1 was shown to bind to human FGF-2 promoter at two sites (−160 and −60). Interestingly, the expression of FGF-2 in human astrocytes was shown to be inhibited by direct cell contact, and the promoter regions related to such density-dependent regulation have been localized to two regions (−650 to −513; −273 to −314). A transactivator was shown to bind to the upstream site (−650 to −513) at low cell density but not at high density. In transformed glialoma cells, such regulation is abolished, and the putative activator binds to the promoter in a density-independent manner (12). The density-regulated FGF-2 expression may explain some differing results obtained from different laboratories studying FGF-2 function and regulation. Because FGF-2 is a potent mitogen, the negative regulation of transcription could likely be an important regulatory mechanism for FGF-2 function; however, to date only the tumor suppressor, p53 protein, has been suggested as a repressor of FGF-2 expression (14).

Here we report the cloning and characterization of a novel transcription factor that represses FGF-2 expression at the transcriptional level. Our data indicate that loss of such regulation may be involved in FGF-2-dependent tumor progression.

EXPERIMENTAL PROCEDURES

**Yeast One-hybrid Screening, Cloning Full-length cDNAs, and Northern Hybridization**—Yeast one-hybrid screening was conducted as described in the manufacturer’s manual (CLONTECH) using human testis cDNA library (17). The three “ggaagaagaaga” tandem repeat was subcloned into pHI5 vector as a reporter plasmid. Full-length RFT cDNAs were cloned by screening human testis cDNA library (CLONTECH) with the radiolabeled cDNAs discovered by yeast one-hybrid screening. All cloned cDNAs were sequenced by an automated sequencer in the DNA sequencing facility at the Salk Institute. Multiple tissue Northern blot membranes (CLONTECH) were hybridized with the same radiolabeled cDNA probes as above.

**Plasmid Construction, Cell Culture, DNA Transfection, Luciferase Assays, and β-Galactosidase Assays**—The His-tagged RFT isoforms were generated by polymerase chain reactions and subcloned into pCDNA3 mammalian expression vector (Invitrogen). RFT-A was generated by digesting RFT-A with AscI, which deleted the sequence encoding the first 111 amino acids. All constructs were sequenced. To generate FGF-2 promoter-luciferase reporter construct (pGL1.2F), 1.2 kb of FGF-2 promoter (18) was subcloned into pGL2-basic vector (Promega). US7MG (ATCC) and 293 cells (19) were cultured in Dulbecco’s modified Eagle’s medium with 10% fetal calf serum in a 5% CO₂ incubator. For DNA transfection, the calcium phosphate method (14) was used for 293 cells and SuperFectant method (Qiagen) was used for US7MG cells. Briefly, 1 × 10⁵ cells were cotransfected with 0.9 μg each of RFT expression vector, 0.9 μg of pGL1.2F, and 0.2 μg of H-RAS-β-galactosidase (20) as a transfection internal control. Luciferase assays and β-galactosidase assays were done as described previously (14). The assays were performed at least three times independently.
RFT Regulates FGF-2 Expression

Immunocytochemistry—Immunocytochemistry was performed to detect overexpressed RFT isoforms and endogenous FGF-2 using anti-His tag monoclonal antibody (1:1000, Qiagen) and anti-human FGF-2 monoclonal antibody (1:20, R&D Systems), respectively. Cy3-conjugated donkey anti-rabbit IgG (1:250, Jackson Immunochemicals) for anti-His antibody and fluorescein isothiocyanate-conjugated donkey anti-goat IgG (1:250, Jackson Immunochemicals) for FGF-2 were used as secondary antibodies. The green fluorescent protein (GFP)-infected cells were visualized by green autofluorescence and stained with the anti-human FGF-2 primary antibody. In this case, Cy3-conjugated donkey anti-goat IgG was used as the secondary antibody to detect FGF-2. The image was analyzed by a confocal microscope and photo modifications were made in Adobe Photoshop 5.0 as follows: His-tagged RFT shown in figures as blue, FGF-2 in red, and GFP in green.

In Vitro Translations and Gel Mobility Shift Assays—For in vitro translations, RFT expression vectors were incubated with [35S]methionine in the rabbit reticulocyte lysate as described in the manufacturer's protocol (Promega). Translated products were separated on an 8% SDS-acrylamide gel and quantified by a PhosphorImager (Molecular Dynamics). The results were adjusted on the numbers of methionine content in each of the RFT isoforms. For electrophoretic mobility shift assay, the same molar amount of each product was incubated with radiolabeled oligonucleotides (20,000 cpm) in the buffer containing 10 mM Hepes, pH 7.5, 50 mM KCl, 1 mM dithiothreitol, 0.1% Nonidet P-40, and 5% glycerol. The oligonucleotide containing RFT binding sequence is gccgaacgccgaacgccgaaccgccgaacgccgaaccgccgaac. The same unlabeled oligo was used as a specific competitor in the assay. A agctagctagctagtacacctgtcctcttccccatctcga oligo derived mainly from FGF-2 promoter (−574 to −597) was used as a nonspecific competitor.

Ribonuclease Protection Assay (RPA)—The partial RFT cDNA obtained through the yeast one-hybrid screening was subcloned into the pBluescript vector (Stratagene). In vitro transcription of the antisense probes and RPA was performed as described in the manufacturer's protocol (Ambion). Briefly, 100 ng of poly(A)+ RNA from human testis (CLONTECH) and 50 μg total RNA from U87MG and 293 cells were hybridized with gel-purified probes (50,000 cpm). The protected bands were loaded on a 5% native gel as double-strand RNAs with the radioactivity hybridized with gel-purified probes (50,000 cpm). The protected bands were loaded on a 5% native gel as double-strand RNAs with the radioactivity. The RFT-A, RFT-A*, RFT-B, and RFT-B isoforms contain two Cys-rich regions. The N-terminal Cys-rich region shows 50% similarity to the human trithorax (HRX) (also called mixed lineage leukemia (MLL) (23) or acute lymphoblastic leukemia (ALL-1) (24) genes). The C-terminus of these proteins is probably formed by a differential splicing mechanism of this exon.

RESULTS

Cloning RFT and Structural Analysis—Human FGF-2 gene has a TATA-less promoter, and its transcript is initiated at only one site (18). We further noticed that a ggcgac sequence is tandemly repeated at both sides of the transcription initiation site of the human FGF-2 gene (Fig. 1A). Using this DNA sequence as bait, we conducted a yeast one-hybrid screening (17). We screened 7 × 106 cDNA clones generated from human testis poly(A)+ RNA. We retrieved two partial cDNA clones that were 447 and 405 bp. Both clones encode an identical cysteine (Cys)-rich region that is a putative zinc finger domain (Fig. 1B).

Because this novel clone may encode a DNA binding protein that binds to FGF-2 promoter, we named this gene the regulator of FGF-2 transcription (RFT). We screened a human testis cDNA library (CLONTECH) using the partial clones as probes. From 12 positive clones isolated, we have obtained full-length clones (RFT-A, and two shorter isoforms, RFT-A' and RFT-B. RFT-A' has a single amino acid deletion at lysine-407 and RFT-B has a deletion of 58 amino acids in the putative DNA binding domain (Fig. 1, B and C). The open reading frame is 1893 nucleotides in RFT-A, 1890 in RFT-A', and 1725 in RFT-B, which encode proteins that are 632, 621, and 574 amino acids, respectively. Based on the genomic DNA sequence (data not shown), RFT-A' is probably formed by a differential splicing mechanism, and RFT-B is formed by an alternative splicing mechanism of this exon.

A structural analysis in Fig. 1C shows that the RFT-A and RFT-A' forms contain two Cys-rich regions. The N-terminal Cys-rich region shows 50% similarity to the human trithorax gene (HRX) (also called mixed lineage leukemia (MLL) (23) or acute lymphoblastic leukemia (ALL-1) (24) genes). The C-terminal...
minal Cys-rich region discovered by the yeast one-hybrid screening, a putative zinc finger domain, shows 50% similarity to the HRX protein and DNA methyltransferase genes (25). The function of the similar region in the HRX gene is not known. The electric charges of the two Cys-rich regions are different, with the N-terminal Cys-rich region being negatively charged and the C-terminal Cys-rich region being positively charged, implicating the C-terminal Cys-rich region as a DNA binding domain. Nine Ser/Thr-Pro-Xaa-Xaa (S/TPXX) motifs are present in all variants of RFT. S/TPXX motifs reportedly are to be found more frequently in gene regulatory proteins and are located on either side of DNA recognizing units (26). In addition, two putative nuclear localizing signals are present near the splicing region.

Expression and Localization of RFT—Northern blot analysis of human multiple tissue shows that the gene is expressed ubiquitously (Fig. 2A). The size of the transcripts on the Northern blot analysis is about 3.0 kb in all tissues, with an approximately 2.6-kb transcript being present in many tissues (Fig. 2A). We performed 3'-rapid amplification of cDNA ends method using RFT-specific primers and human testis poly(A) RNA. The results indicate that the difference in size of these transcripts was attributable to an alternative splicing in the 3'-untranslated region, suggesting a potential instability of mRNA (data not shown).

In vitro translated products of RFT-A, RFT-A', and RFT-B forms migrate at the molecular weight of approximately 90, 90, and 75 kDa, respectively, on a denaturing gel (data not shown).

To determine the localization of each form of RFT in cells, we constructed His-tagged expression vectors of each form and transfected them into the human glioma cell line, U87MG (ATCC), and the human kidney tumor cell line, 293 (18). After staining by anti-His tag antibody, a confocal microscopic analysis study showed clear nuclear localization of all forms in each cell line (Fig. 2B).

Next, to determine the affinity specificity of each form to the gccgaac sequence, we performed gel mobility shift assays. The RFT-A form shows highly specific affinity to gccgaac sequence, and the RFT-A' and RFT-B forms show undetectable affinity to the same sequence (Fig. 3A). Thus, the structural examination, the localization study, and the DNA binding assay support the suggestion that the RFT gene product is a nuclear protein, and it may function as a transcription factor.

**RFT-A Represses FGF-2 Expression**—To investigate the
function of the RFT gene, we performed co-transfection using the expression vectors for each RFT isoform and pGL1.2 F carrying a 1.2-kb fragment of FGF-2 promoter fused with luciferase gene as a reporter construct into the U87MG and 293 cells. As an internal control, H-Ras β-galactosidase (19) was also transfected. After 40 h, luciferase and β-galactosidase assays revealed that, in the U87MG cell lines, the RFT-A form repressed the 1.2 kb of FGF-2 promoter activity more than 10-fold; in the 293 cell line, RFT-A nearly completely repressed 1.2 kb of FGF-2 promoter activity. By contrast, RFT-A’ and RFT-B did not repress but rather induced a small activation of the FGF-2 promoter in the 293 cell line and, to a lesser extent, in the U87MG cell line (Fig. 3B). In both cell lines, a dose-dependent effect of all forms of the RFT was observed (data not shown). To investigate if the transcriptional repression of RFT-A is specific for FGF-2 promoter, we did co-transfection using RFT expression vectors and epidermal growth factor receptor promoter-luciferase construct. RFT-A does not affect epidermal growth factor receptor promoter activity that does not have the gccgaac motif (data not shown).

To determine whether the RFT gene product could regulate the endogenous FGF-2 gene expression, reverse transcriptase PCR in the linear range was performed on the two cell lines after the cells were infected with an engineered AAV carrying the green fluorescence protein gene (CLONTECH) (AAV-GFP) was used as a control. This is the first negative regulator for FGF-2 that has been shown to bind a definitive sequence in FGF-2 promoter. Given the significance of FGF-2 in development, neurological diseases, and tumor formation, dis-
overexpression of RFT-A, RFT-A', RFT-B, and RFT-ΔA. Cells were immunostained with anti-His tag (blue) and anti-FGF-2 (red) antibodies to localize the RFT proteins and to measure relative levels of FGF-2 protein, respectively. AAV-GFP infected cells were used as a control, and GFP is shown in green. Untreated cells are also included as Control.

**Fig. 4. Biological function of the RFT gene.** Immunocytochemical analysis of U87MG and HEF cells by a confocal microscope after overexpression of RFT-A, RFT-A', RFT-B, and RFT-ΔA. Cells were immunostained with anti-His tag (blue) and anti-FGF-2 (red) antibodies to localize the RFT proteins and to measure relative levels of FGF-2 protein, respectively. AAV-GFP infected cells were used as a control, and GFP is shown in green. Untreated cells are also included as Control.

**Fig. 5. Biological function of the RFT.** A, ribonuclease protection assays for the detection of each of the RFT isoforms in tumor cell lines and testis. Probes used for the assay are indicated. The size of protected bands is shown by the DNA marker (bp). B, phase contrast images of cells 96 h after RFT-AAV infection. 40× microscope images indicate that RFT-A induces U87MG cell death, whereas the other forms or GFP do not. The lower panel in AAV-A demonstrates cell death determination by a confocal microscopic image of TdT-mediated dUTP-X nick end-labeling (TUNEL) staining in green for cells infected with RFT-AAV-A. Positive TUNEL staining was observed at 72 h postinfection and peaked at 96 h. Note that RFT-B infected cells grow in clusters.

covery and understanding of such a factor bring us closer to the understanding of FGF-2-dependent cellular processes.

**RFT Represses the Expression of FGF-2**—Our data have shown that RFT can bind to the specific gccaaga sequence and reduces the promoter activity and endogenous RNA (Fig. 3) and protein (Fig. 4) levels of FGF-2. Taking these results together with the nuclear localization of each RFT form (Fig. 3A), we conclude that RFT-A is a transcription factor that can bind to the basal core promoter of the FGF-2 gene and repress the promoter activity. The working hypothesis is that RFT binds to the gccaaga sequence and blocks the binding of RNA polymerase II to the transcriptional initiation site. How such repression is regulated under physiological conditions is unknown.

**Splice Variants of RFT**—Alternative splicing, which happens in 1 of 20 genes, plays important roles in diversifying cellular gene regulation. Splice variants often have different expression patterns and carry different physiological functions (29–31). In several well characterized cases, splice variants either serve as dominant negative regulators by competing with the same effector or serve as traps by forming a dimer with the active form. For example, ITF-2, a basic helix-loop-helix protein, forms an active dimer with MyoD, but its splice variant ITF2B inhibits the function of ITF-2 by forming an inactive dimer with MyoD (32). ATFα, an ATF/CREM family transcription factor, has a splice variant, ATFα-O, that inhibits ATFα function by forming heterodimers (33).

The splice variants of RFT, RFT-A', and RFT-B contain defective DNA binding domains and fail to bind the gccaaga sequence and repress FGF-2 transcription. This lack of function is attributable to the mutations in their DNA binding domain and is likely caused by alternative splicing but not to the disruption of the nuclear localization signal. So far, the functions of RFT-A' and B are not fully understood. Because the RFT binding sequence is a tandem repeat, RFT-A may form a dimer to bind to FGF-2 promoter. In such a case, RFT-A' and B may inhibit RFT-A function by forming a heterodimer, as in the case of ATFα. In Fig. 3, B and C, RFT-A' and B induce a slight activation in both U87MG and 293 cells, but there is a difference in the magnitude of responsiveness for RFT-A' and RFT-B between the U87MG and 293 cell lines. We hypothesize that this difference might be because of the difference in endogenous levels of each RFT isoform between the two cell lines. Our interpretation is that high endogenous RFT-A' and RFT-B levels in U87MG cells have a more dominant negative effect on cellular RFT-A; therefore, exogenous RFT-A' and B in U87MG cells are less effective than in 293 cells.

When we measured the protein level of FGF-2 after overexpression of RFT, we saw that FGF-2 level is nondetectable in RFT-A-infected cells. However, in RFT-B-infected cells, some cells continue to show a high level expression of RFT-B. These results indicate that, unlike RFT-A, RFT-B overexpression is not incompatible with FGF-2 expression.

It appears that, at least proportionally, transformed glial cells express more mutant forms of RFT (A' and B) than the functional form (A) (Fig. 5). We do not know if this is the cause of the transformation or a middle step or the result of tumor progression. Our data suggest that these splice variants could be either dominant negative regulators of RFT-A or by-products of mistaken alternative splicing. We are currently conducting experiments to investigate this issue.

**RFT-A Causes Glioma Cell Death**—Most human gliomas are characterized by high level expression of FGF-2. However, it is not known if overexpression of FGF-2 is the direct cause of tumorigenesis and progression. Previous data have shown that anti-FGF-2 neutralizing antibodies cause glioma cell apoptosis (28).

In our studies, introducing high level RFT-A carried by AAV into glioma cells also decreases intracellular FGF-2 level and
causes cell death. The positive TUNEL staining suggests that the cells may undergo apoptosis, but at present we are exploring the mechanism of cell death further. Interestingly, overexpression of RFT-B, which is a dominant form of RFT in human glioma, not only did not cause cell death but also increased cell growth into proliferative aggregates of cells that piled upon each other (Fig. 5B). Such an effect may be because of the activating function of RFT-B as shown in transient transfection assay (Fig. 3B). Moffet et al. (12) observed that factors in human astrocytes bind to FGF-2 promoter in a cell density-dependent manner and induce contact inhibition. The function of RFT suggests that it may be one of the candidates for such factors. Therefore, our data suggest that even though FGF-2 may not be the original cause of tumor progression, it may be a key player in this process. An abnormally high level of FGF-2 may result from the lack of RFT-A expression relative to RFT-A' and B. If such a hypothesis is proven to be correct, we speculate that RFT-A could be a useful agent in treating FGF-2-dependent tumors.

In conclusion, FGF-2 gene expression is negatively regulated by RFT-A by transcriptional repression. Regulation of such function is partly achieved through the alternative splicing mechanism in the DNA binding domain of RFT, suggesting that the imbalance in the ratios of these splice variants may be responsible for the constitutive expression of FGF-2 gene, resulting in tumor progression in FGF-2-dependent tumors. Furthermore, overexpression of the normal transcriptional repressor, RFT-A, induces apoptosis when FGF-2 is deregulated in tumor cells.

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