Human α(1,3)-Fucosyltransferase IV (FUTIV) Gene Expression Is Regulated by Elk-1 in the U937 Cell Line*

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The α1,3-fucosyltransferase IV (FucTIV) encoded by its gene (FUTIV) is responsible for synthesis of Lexα (Galβ4[Fucα3]GlcNAcβ3Galβ1,R), which causes compaction in the morula stage of the preimplantation mouse embryo, as well as α1,3-fucosylation at multiple internal GlcNAc of unbranched poly-N-acetyllactosamine, termed “myeloglycan,” the physiological epitope of E-selectin. Since myeloglycan-type structure is also expressed in various types of human cancer and may mediate E-selectin-dependent metastasis, expression of FUTIV is oncodevelopmentally regulated. The mechanisms controlling FUTIV expression remain to be clarified. In this report, we further characterize FUTIV gene structure and define a non-TATA box-dependent transcriptional start region just upstream from the translational start. FUTIV promoter/reporter fusion constructs defined a “full-length” promoter and highly active fragments in the macrophage-derived U937 and myeloid HL60 cell lines. One highly active fragment contains a consensus binding site for the Ets-1 transcription factor (Withers, D. A., and Hakomori, S. (1997) Glycoconjug. J. 14, 764). Gel shift analysis shows specific binding to this site in nuclear extracts from U937 cells. Mutation of the Ets consensus site significantly reduces FUTIV promoter activity in both cell lines. Gel supershift and dominant negative cotransfection experiments identified the Ets family member Elk-1 as one component binding and regulating the FUTIV promoter in U937 cells. The significance of FUTIV regulation by Elk-1 is discussed.

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The nucleotide sequence(s) reported in this paper has been submitted to the GenBank®/EBI Data Bank with accession number(s) AF305082 and AF305083.

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The abbreviations used are: FucT, fucosyltransferase; RT, reverse transcription; PCR, polymerase chain reaction; EMSA, electrophoretic mobility shift assay; kb, kilobase pair(s); RACE, rapid amplification of cDNA ends.

in embryonal carcinoma F9 cells is due to expression of the FUTIV gene (1). Leα at morula stage is thought to cause compaction, the first cell adhesion event during embryogenesis, in which Leα-Leα interaction plays a major role (2, 3) prior to uvomorulin (cadherin)-dependent adhesion (4). Cell adhesion based on Leα glycolipid was confirmed recently (5). FucTIV is also involved in synthesis of the cell surface epitope, so-called myeloglycan, consisting of unbranched long chain type 2 poly-N-acetyllactosamine having α1–3 fucosylation at multiple internal GlcNAc with α2–3 sialylation at terminal Gal (6). Myeloglycan is considered the major physiological E-selectin epitope controlling tethering and rolling of neutrophils on solid phase E-selectin, particularly under dynamic flow conditions (7). Expression of FucTIVII is responsible for α1–3 fucosylation at penultimate GlcNAc, but penultimate fucosylation by FucTIVII is inhibited by internal α1–3 fucosylation by FucTIV. Thus, FucTIV is responsible mainly for synthesis of myeloglycan without fucosylation at penultimate GlcNAc, i.e., without sialyl-Leα (8). Various types of tumor express myeloglycan-type structures (9), which may mediate E-selectin-dependent metastasis (for review, see Ref. 10).

Expression of the α1,3-FUT gene family has been examined for lung (11), colorectal (12, 13), and gastric (14) tumors. In all cases, FUTIV expression is significantly higher in tumors than in adjacent non-tumorous tissue. In lung tumors, FUTIV and FUTVII expression levels were inversely correlated with patient prognosis (11). FUTIV expression has also been studied in purified myeloid lineage cells and cell lines induced to differentiate (15–17). Typically, differentiated cells lose surface Leα expression accompanied by a decrement in FUTIV transcript levels as compared with undifferentiated cells. Conversely, the colon adenocarcinoma cell line HT-29 shows elevated FUTIV mRNA levels when apoptosis is induced (18).

The collective data suggest that Leα, determined by “myeloid type” fucosyltransferase (FucTIV) expression, is an oncofetal marker. Expression is regulated during normal development (16, 19, 20) and in tumors (11–13). We sought to identify the trans-acting factors responsible for up-regulating FUTIV expression in tumor cell lines. Preliminary studies localized upstream genomic DNA fragments with high promoter activity in U937 and HL60 tumor cell lines (21). The data presented here identifies the Ets family member Elk-1 as a positive regulatory factor acting on the FUTIV promoter in U937 cells.

MATERIALS AND METHODS

Isolation of FUTIV Genomic DNA, Plasmid Construction, and Sequence Analysis—A FUTIV genomic clone, a20, was isolated from a human placental genomic DNA library (Stratagene) while screening with a FUTIII probe. The EcoRI/NcoI 3.1-kb and BamHI/NcoI 1.65-kb

‡‡FUTIV promoter deletion analysis identified a highly active region containing an Ets transcription factor consensus binding site, as reported at the First International Symposium on Fucosyltransferases and Cellular Communications, Mar 26–28, 1997, Osaka, Japan (21).
fragments from x20 were cloned into the luciferase reporter vector pGL3basic (Promega) to make pG-3092Eco and pG-1647Bam, respectively. Using unique restriction sites, deletion derivatives of these constructs were made by simple digestion and recircularization.

The consensus Ets-1 site at −350 (from the translational start site) was mutated in promoter fusion constructs using the recombinant PCR technique (22). Primary PCR reactions used the −518 (XhoI/NcoI) construct in the pOGH vector (Nichols Institute, San Juan Capistrano, CA) as template. 3′-Primary PCR used a mutated Ets-1 site primer, ELMmut (−361 to −338; 5′-GGGCAGGCGGCCATGGCCTGCCCGG-3′, mutated bases underlined), and a downstream vector primer (5′-TGCACTAGGTCAGGCACCT-3′). 3′-Primary PCR was amplified (complementary to 3′ELMmut) and an upstream vector primer (5′-CCACGTCAAGCAGTGGTAACG-3′). Secondary PCR used primary PCR fragments as templates and the flanking vector primers. The resulting fragment was digested with BstXI and SfI and cloned into pG-1647Bam deleted for BstXI/SfI. Resulting clones were sequenced through the BstXI/SfI site interval. DNA was sequenced either manually using Sequenase version 2.0 (Amersham Pharmacia Biotech) or with an ABI310 automated sequencer. Putative promoter sequences were analyzed for consensus transcription factor binding sites using Transcription Element Search Software (TESS) (23).

RT-PCR was performed using the Titan® one-tube RT-PCR kit (Roche Molecular Biochemicals) according to the manufacturer’s instructions. HL60 RNA samples were treated with RNase-free DNase (RNase-free; Promega Corp.) or RNase (prepared by boiling for 5 min; DNase-free) to confirm absence of DNA-based PCR. PCR used the following constructions. HL60 RNA samples were treated with RQ1 DNase (RNase-controlled) according to the manufacturer’s instructions. Firefly luciferase levels were determined on a EG&G Berthold Lumat LB 9507 luminometer with a 100-µl v-liter injection. Growth hormone levels were assayed from the culture medium using the HGH-TGES kit purchased from Nichols Institute (San Juan Capistrano, CA). Extract protein levels were determined by the bicinchoninic acid method (Pierce). Luciferase activity was normalized by both growth hormone (transfection efficiency control) and protein levels (cell number control).

RESULTS

FUTIV Gene Structure—The FUTIV gene produces three transcripts of 2.3, 3.0, and 6.0 kb as detected on Northern blots (15, 28, 29). The 2.3- and 6.0-kb transcripts are typically detected at much higher abundance than the 3.0-kb species (Fig. 2B). cDNA sequences corresponding to the 2.3- and 3.0-kb transcripts were described previously (28) (see Fig. 1). The derivation of the 6.0-kb transcript, however, is not known and has been suggested to come from an as yet undescribed FUT gene. This possibility led us to further investigate FUTIV gene structure. DNA sequence of a FUTIV 3′-genomic DNA fragment and the FUTIV 3′-untranslated region (Fig. 1) were used to synthesize downstream and upstream primers, respectively, for RT-PCR amplification of the putative 6.0-kb transcript. This experiment, shown in Fig. 2A, clearly detects the presence of another FUTIV transcript containing sequences common to the 3.0- and 2.3-kb FUTIV transcripts (since the upstream primer falls within the 3′-untranslated region of the 2.3- and 3.0-kb transcripts) as well as additional 3′-untranslated sequences. In addition, this RT-PCR-generated fragment detects only a 6.0-kb transcript on Northern blots (Fig. 2B).

Using 3′-RACE analysis (24), the remainder of this cDNA...
was cloned. Sequence analysis showed a 3,098-base pair extension from the 3' most sequences of the 3.0-kb transcript (ELFT-L) to the poly(A) addition site. This cDNA is colinear with genomic DNA (data not shown). The 6.0-kb transcript, which matches previously unassigned clones in the human expressed sequence tag data base, uses an alternate poly(A) which matches previously unassigned clones in the human with genomic DNA (data not shown). The 6.0-kb transcript, (ELFT-L) to the poly(A) addition site. This cDNA is colinear with genomic DNA (data not shown). The 6.0-kb transcript, which matches previously unassigned clones in the human expressed sequence tag data base, uses an alternate poly(A) addition site from the shorter expressed sequence tag data base, uses an alternate poly(A) which matches previously unassigned clones in the human with genomic DNA (data not shown). The 6.0-kb transcript, (ELFT-L) to the poly(A) addition site. This cDNA is colinear with genomic DNA (data not shown).

Promoter Analysis—A genomic clone containing FUTIV was isolated from a placental DNA library (CLONTECH) using FUTIII gene sequences as probe. 3.1 kb extending upstream from the start of translation was subcloned and sequenced (Fig. 3). This fragment matches the restriction map of the FUTIV upstream region (29–31) and contains 5' sequences from the FUTIV 2.3- and 3.0-kb cDNAs (28) (Fig. 1), thus confirming its identity as FUTIV. Comparison of the FUTIV upstream sequence to a transcription factor consensus binding site data base revealed many matches to described factor binding sites (Fig. 3).

The 3.1-kb fragment was cloned into the luciferase reporter vector (pGL3basic) to make “pG-3092Eco.” This “full-length” fragment and deleted or mutated derivatives were transfected into FUTIV-expressing cell lines U937 and HL60, and luciferase reporter levels were assayed. The longest constructs (pG-3092Eco, pG-2444Nsi, and pG-2145Pac) have undetectable promoter activity in both cell lines (data not shown). Deletion derivatives, such as pG-1800HindIII (data not shown) and pG-1647Bam have high activity in U937 (Fig. 4) and HL60 (data not shown) cell lines. In addition, the internal deletion removing sequences from -424 to -273 from the full-length promoter has significantly reduced activity in U937 cells. Mutation of a consensus Ets-1 binding site at position -350 reduces promoter activity further (Fig. 4). This region was further studied using EMSA in order to localize potential transcription factor binding sites.

Electrophoretic Mobility Shift Assays Using the Ets Consensus Site at -350—The 151-base pair interval from -424 to -273 contains a consensus binding site for the Ets family of transcription factors located at -350. Oligonucleotides corresponding to FUTIV promoter region -350 and containing wild type or mutant Ets binding sites were used in EMSA to detect binding activity in U937 cells (Fig. 5). The Ets mutant oligonucleotide differs from wild type by a three-base substitution at the Ets consensus core sequence (see “Materials and Methods”). At least two binding activities (see s1 and s2 in Fig. 5) were detected with the wild type oligonucleotide. These activities were specific for the Ets consensus site since binding was competed with excess unlabeled wild type, but not mutant, oligonucleotide (Fig. 5, left panel, lanes 2 and 3). In addition, s1 and s2 bands were absent when the mutant oligonucleotide was used as probe (Fig. 5, left panel, lane 4).

The identity of the factor(s) bound to the FucTIV Ets consensus site was investigated using EMSA and antibodies to various Ets family members (Fig. 5, middle panel). The most abundant specific binding activity (s2) is shifted in mobility upon addition of anti-Ets-1 antibody to the binding reaction (middle panel, lane 3). Ets-1, p41 (middle panel, lanes 2 and 4, respectively), Ets-2, and SAP-1 antibodies failed to recognize U937 nuclear proteins bound to this site (data not shown). In addition, the s2 band is absent from FUTIV-nonexpressing HepG2 cells (Fig. 5, right panel).

Role of the Elk-1 (−350) Binding Site—A promoter fusion construct (pG-1647Bam/−350(Elk1)) was made containing the same Ets-1 site mutation used above for EMSA. When compared with wild type (pG-1647Bam), promoter activity of the Elk-1 site mutant is significantly reduced in U937 cells (see Fig. 4).

The role of Elk-1 was further investigated by co-transfection experiments using the FucTIV promoter fusion construct pG-1647Bam, containing either the wild type or mutated Elk-1 −350 site, along with an expression vector encoding dominant
Elk-1 Regulates Human FUTIV

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We have localized the predominant promoter for the FUTIV gene to just upstream from the translational start site. The FUTIV promoter lacks a TATA box and fits the criteria of a CpG island (50). Typical of such promoters, multiple, scattered transcriptional start sites were identified. In addition, a key regulator of the FUTIV promoter, Elk-1, was identified by DNA binding and cotransfection experiments.

Elk-1 was originally found by homology with the oncogene for Ets-1 (51) and is a member of the large family of Ets-related transcription factors. The Ets family regulates expression of other glycosyltransferases such as β4-galactosyltransferase-I by TASS-I (52), β-1,2-N-acetylgalactosaminyltransferase II and N-acetylgalactosaminyltransferase-V by Ets-1 and Ets-2 (53–56), as well as members of the metalloproteinase gene family (57–61). Activity of N-acetylgalactosaminyltransferase-V and metalloproteinases contributes to the metastatic capacity of tumors.

Ets family proteins bind to DNA either autonomously or as a member (called the ternary complex factor) of a complex with the dimeric serum response factor. Three Ets family members are capable of acting as ternary complex factors (Elk-1, SAP-1, and SAP-2/Erp/Net; reviewed in Ref. 62). Ets family proteins bind DNA sites containing a core GGA consensus sequence via a winged helix-turn-helix DNA binding motif (reviewed in Ref. 63). Binding site specificity for members of the Ets family is partially determined by DNA sequence flanking the core site. The FUTIV Elk-1 binding site at −350 (GCCCGGAGGCC) matches the 7 central bases of the 11-base consensus sequence (AACCGGAAGTG/a) to which Elk-1 binds autonomously (64). The latter sequence was also selected from randomized oligonucleotides by the Elk-1 DNA binding domain (65). SAP-1 is theoretically capable of autonomous binding to the FUTIV −350 site (65) but does not occur in U937 extracts (data not shown), so the identity of the s1 binding activity seen in Fig. 4 is unknown. Since a serum response element is absent in the promoter region, Elk-1 may bind to this site autonomously rather than as a component of serum response factor. If so, this is the only functional gene promoter site yet described capable of autonomous regulation by Elk-1.

Elk-1 is a target of central importance in both Ras-dependent and -independent mitogen-activated protein kinase signaling pathways in numerous cell types (32, 66–69). Both growth factor-regulated kinases and two groups of stress-activated kinases (c-Jun N-terminal kinases and p38 kinase) have been

**FIG. 3.** Sequence of 3′ portion of the FUTIV promoter. Numbering corresponds to distance 5′ to the start of translation (underlined). Boldface and thin arrows show high frequency start sites (9 of 11 independent RACE clones for −96 and −88 sites combined), and thin arrows show low frequency start sites at −129 and −145 (one RACE clone each).

**FIG. 4.** Bar graph showing relative activity of pG-1647(Bam) versus pG-1647((Bam −350Elk′)) versus pG-1647(Bam Δ 424/−273) versus pG basic in U937 cell line. Extracts were prepared from each sample and luciferase, growth hormone, and protein levels assayed. Luciferase activity was normalized by both growth hormone (transfection efficiency control) and protein levels (cell number control). Normalized activities are expressed relative to the pGbasic sample, which was arbitrarily assigned the value 1.0. Plotted values represent the average of at least three independent experiments for each construct.

**DISCUSSION**

negative Elk-1 protein (32). Results of these experiments are shown in Fig. 6. The data show a dramatic reduction (approximately 5-fold) in promoter activity of the pG-1647Bam construct when co-transfected with the dominant negative Elk-1, but not the empty vector plasmid. When the mutant Elk site construct was used as reporter, DN-Elk cotransfection encoding, but not the empty vector plasmid. When the mutant Elk site construct was used as reporter, DN-Elk cotransfection approximately 5-fold) in promoter activity of the pG-1647Bam construct. The latter data suggest that Elk-1 binds to and regulates other sites in the FUTIV promoter.

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found to activate Elk-1 (32, 70–72). Phosphorylation of Elk-1 induces a conformational change that increases its DNA binding, transcriptional activating and serum response factor binding activities, thus activating both the ternary complex and autonomous transcriptional regulatory functions of this protein (32, 66, 73, 74). The multiplicity of signaling pathways that activate Elk-1, and their deranged regulation in tumors, may explain the common expression of an autonomous Elk-1 target such as FUTIV in many tumors and tumor cell lines of various derivation (38, 43). In contrast, adults express the myeloid-type fucosyltransferase activity attributed to FucTIV only in adult human leukocytes and brain tissue (20).

Whether Elk-1 plays a role in FUTIV expression during normal development is not known. It is of interest, however, that a fucosyltransferase activity with acceptor and inhibitor specificity characteristic of FucTIV is expressed in the early stages of development of many human tissues. The embryonic fucosyltransferase activity gives way to a distinct tissue characteristic activity in the adult organ (20). This expression pattern is mirrored in the developing myeloid lineage, where immature promyelocytes express predominantly FUTIV while mature granulocytes express mostly FUTVII but very low levels of FUTIV (15). The developing human lung also shows stage specific patterns of Leα, Leβ, and SLeα expression. Leα is abundantly expressed in the early developmental stages, in cells of the presumptive bronchiolar, but declines in abundance after overt development of this tissue (19). Finally, down-regulation of FUTIV mRNA levels is seen upon MeSO4-induced differentiation of the promyelocytic HL60 cell line (16). Recently, a sixth α1,3-fucosyltransferase (FucTIX) (39) has been described, which apparently shares acceptor specificity and NEM insensitivity (see analysis in Ref. 40) with FucTIV. Although some of the above studies specifically assay FUTIV mRNA expression (by RT-PCR), caution is warranted in attributing enzyme activity or end product (Leα) expression to FucTIV. Given all this information, it is likely that Elk-1 plays a role in establishing or maintaining expression of FUTIV in embryonic tissues or pluripotent lineages, but our data do not support a role for Elk-1 in FUTIV down-regulation during differentiation (data not shown).

Cell surface, stage-specific embryonic expression of Leα, determined by FucTIV activity, may mediate cell adhesive interactions during tissue morphogenesis. Evidence in support of this comes from studies of mouse preimplantation embryos, the blastomeres of which normally have a tightly compact form, but undergo decompaction when incubated with multivalent Leα in solution (75, 76). Blastomere compaction is known from gene knock-out experiments to be mediated by E-cadherin (77). Using mutant embryocarcinoma (EC) cell lines, other molecules involved in this process have been identified. Cells from two independent mutant lines, deficient either for embryoglycan (the major carrier of Leα in EC cells (Ref. 78)) or for α(1,3)-fucosyltransferase activity, could not aggregate with wild type cells (48, 79), despite a normal capacity for homotypic aggregation. These studies suggest that cell surface Leα plays a role in the initial stages of E-cadherin-mediated cell adhesion.
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