Transcription of the Human Colony-Stimulating Factor-1 Receptor Gene Is Regulated by Separate Tissue-Specific Promoters

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Receptors for macrophage colony-stimulating factor (CSF-1R) are expressed not only by monocytes, macrophages, and their progenitors, but also by placental trophoblasts during fetal development. In monocytes, CSF-1R gene transcripts originate at multiple sites immediately upstream of the gene's coding sequences, whereas in placental cells the transcripts include an additional noncoding exon, located 28 kb upstream near the 3' end of the B-type platelet-derived growth factor (PDGF) receptor gene. Physically distinct CSF-1R transcription origins suggest separate promoter usage by the two cell types. To identify regulatory elements of these promoters, we fused CSF-1R genomic sequences to bacterial reporter genes and introduced the resulting constructs into human cell lines and mouse fibroblasts. A 775-bp genomic fragment containing CSF-1R placental transcription origins and adjacent upstream sequences mediated reporter gene expression in BeWo choriocarcinoma cells and mouse NIH-3T3 fibroblasts, but not in myeloid or lymphoid cells. By contrast, a 550-bp genomic fragment containing CSF-1R monocyte transcription origins and five flanking sequences directed gene expression in U-937 human myeloid cells, but not in the other cell types. Thus, nucleotide sequences of fewer than 1,000-bp upstream of the two independent CSF-1R transcription origins contain the minimal promoter elements needed to program appropriate tissue-specific expression of reporter genes.

The proto-oncogene c-fms encodes the cell surface receptor for the macrophage-colony-stimulating factor (CSF-1 or M-CSF), a lineage-specific hematopoietin whose actions are required for the growth and survival of cells of the mononuclear phagocyte series. Cell surface expression of the CSF-1 receptor (CSF-1R) begins when myeloid progenitors commit to development within the mononuclear phagocyte lineage and increases as the cells mature. CSF-1 receptors are also expressed by placental trophoblasts during gestation, as CSF-1 production by uterine epithelium increases nearly 1,000-fold. Thus, CSF-1R and its receptor may have a role in placental development.

Studies of the CSF-1R gene indicate that its expression is regulated differently in myeloid cells and placental trophoblasts. We showed that placental CSF-1R transcripts include a noncoding exon located 26 kb upstream from the receptor-coding sequences, and less than 0.5 kb from the 3' end of the B-type platelet-derived growth factor receptor gene (PDGF-Rβ). Visvader and Verma subsequently found that the upstream CSF-1R exon is not transcribed in cells of the monocyte lineage; rather, such transcripts originate from contiguous sequences immediately upstream of the initiator codon. Different transcription origins suggest separate promoter usage by the two cell types, although evidence of functional activity by discrete CSF-1R promoters is lacking. The studies described here identify the initiation sites of CSF-1R transcripts in monocytes and choriocarcinoma cells, and demonstrate tissue-specific expression of bacterial reporter genes in monolayer cell lines transfected with constructs containing less than 1,000 bp of genomic DNA upstream of each transcription origin.

MATERIALS AND METHODS

Cell lines and tissues. Four cell lines—U-937 (human myeloid leukemia), Molt-4 (human T-lymphoid leukemia), BeWo (human choriocarcinoma), and NIH-3T3 (mouse fibroblasts)—were used. Nonadherent cell lines were grown in RPMI-1640 medium, while adherent lines were maintained in Dulbecco's modified Eagle's medium, each supplemented with 10% fetal calf serum. In some experiments, U-937 cells were incubated for 72 hours in medium containing 12-O-tetradecanoylphorbol-13-acetate (TPA; Sigma Chemical Co, St Louis, MO) at a final concentration of 10−7 mol/L. Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque density centrifugation as previously described.

RNA extraction and Northern blot analysis. Total cellular RNA was isolated by the guanidinium/cesium chloride method. RNA samples separated by electrophoresis in a 1% agarose gel containing 2.2 mol/L formaldehyde were transferred to a nylon membrane. Radiolabeled plasmids containing the 4-kb human c-fms cDNA and B-actin sequences were hybridized to the blot sequentially according to procedures described by Thomas.

cDNA cloning. An anchored polymerase chain reaction (PCR) procedure, RACE, described by Frohman et al, was used with minor modifications to clone cDNA molecules representing the 5' ends of CSF-1R transcripts. A CSF-1R-specific cDNA template was synthesized with reverse transcriptase from both monocyte and BeWo cellular RNAs by use of an oligonucleotide primer that was inversely complementary to sequences near the 5' end of the previously characterized CSF-1R cDNA (5'-3': CAGGCTCGAGGCTGCGCC5'). Excess 5'-RT oligonucleotide was removed by passing the cDNA reaction mixture over a Bio gel A-5M column (BioRad, Rockville Centre, NY); single-stranded cDNA templates were polyadenylated with terminal transferase. The second cDNA strand was synthesized with thermostable Tag I polymerase, using a 34-nucleotide dT17-adaptor primer that contained unique restriction sites for subsequent cloning. The cDNA products were amplified with the adaptor primer and a primer containing sequences inversely complementary to CSF-1R sequences just upstream of the 5'-RT primer (5'-3': CAGGTCAGGCTGCGCC5'). The PCR products were digested with Sac I and Sal I.
restriction enzymes, which cut within known cDNA sequences and the adaptor sequences, respectively. The digested products were cloned into the SK’ Bluescript vector (Stratagene, San Diego, CA), and clones that hybridized with a CSF-1R exon 2 probe were sequenced by the dideoxy chain-termination method.24

S1 nuclease protection assays. S1 mapping was performed by the method of Berk and Sharp,25 as modified by Weaver and Weissman,26 using end-labeled DNA probes. To detect initiation sites of endogenous CSF-1R transcripts, we prepared two probes that contained sequences from the exon 1 and 2 regions. Probes containing genomic fragments fused to the neomycin resistance gene (neo8) were used to detect initiation sites of transcripts produced in transfected cells. Cellular RNAs (100 μg) were hybridized with the end-labeled DNA fragments, digested with 150 units of S1 nuclease, and analyzed by autoradiography after electrophoresis in 8% polyacrylamide gels. The lengths of each protected fragment were determined by comparing their mobilities to a known sequenced standard using the Sizer computer program (IntelliGenetics, Mountain View, CA).

Construction of plasmids containing genomic sequences linked to bacterial reporter genes. A 550-bp Sac I fragment containing CSF-1R monooyte transcript origins and a 775-bp BamHI fragment containing placental transcript origins were tested for promoter activity. The 3’ BamHI site within CSF-1R exon 1 was introduced by PCR to facilitate cloning. These fragments were introduced into the promoterless and enhancerless pCAT3M plasmid27 in both sense and inverse orientation immediately upstream of the bacterial chloramphenicol acetyltransferase (CAT) gene. Plasmids that linked the two genomic fragments in appropriate orientation 5’ to the neo8 gene were also constructed.28,29 The ability to detect transcription initiated by genomic fragments was enhanced by constructing plasmids with an exogenous viral SV40 core enhancer,30,31 positioned 3’ to either the CAT (pCAT/SV40) or neo8 gene.

Transfection of recombinant plasmids. Test and control plasmids were introduced with carrier DNA into NIH-3T3 cells by the calcium phosphate precipitation method, as previously described,35 and into U-937, Molt-4, and BeWo cells by electroporation. Electroporation was performed with RPMI used as the conductance media; in each experiment, a discharge of 170 V and 960 microfarads was delivered to 2 × 107 U-937 or Molt-4 cells, and 500 V and 25 μF to 5 × 106 BeWo cells. For CAT assays, equal molar amounts of each CAT plasmid and a control β-galactosidase expression plasmid were cotransfected; cell lysates were harvested at 48 hours for transient expression analysis. Stable transfectants were generated by introducing plasmids containing the neo8 gene into cells followed by culture in medium containing G418. G418-resistant cells were pooled and grown for RNA extraction for the S1 nuclease assay.

CAT and β-galactosidase assays. Assays to detect CAT enzymatic activity were performed as described by Gorman et al.34 Cell lysates were incubated with [3H]chloramphenicol (Amersham, Arlington Heights, IL), and products were separated on silica gel thin-layer chromatography plates in chloroform:methanol (95:5 vol/vol); exposed autoradiograms were analyzed by scanning densitometry. A second method to quantitate CAT activity was performed by incubating cell lysates with [14C]acetetyl CoA (New England Nuclear, Boston, MA) as previously described by Neuman et al.35 The lysate reaction mixture was overlaid by a toluene-based scintillation fluid, and acetylated products were counted at 4, 8, and 24 hours. The two methods were comparable in the quantitation of CAT enzymatic activity. Transfection variability was controlled by performing electroporations in triplicate. Furthermore, each cell lysate was simultaneously analyzed for CAT enzyme activity and control plasmid β-galactosidase activity, as described by Herbmole et al.36 The measured CAT activity was normalized relative to β-galactosidase activity. The results for each CAT plasmid tested represent the mean average for three assays and are expressed as the percentage of CAT/β-galactosidase activity relative to the positive pCMV CAT control.

RESULTS

Northern blot analysis of CSF-1R transcripts. RNAs from the human cell lines were hybridized with a CSF-1R cDNA probe to detect steady-state levels of mRNA (Fig 1). The BeWo choriocarcinoma line, a malignant counterpart of placental trophoblasts, was selected as a model of CSF-1R transcription in cells of placental origin. BeWo cells expressed transcripts with mobilities similar to those of monocytes (Fig 1). The U-937 myeloid leukemia line was chosen to study promoter activity in cells of the monocytic lineage for the following reasons. These cells do not have detectable CSF-1R transcripts when grown under standard conditions (Fig 1), but do exhibit monocytoid features, including CSF-1R expression, when stimulated with TPA.37 TPA treatment does not increase the rate of CSF-1R transcription but rather acts by increasing transcript stabil-
The Molt-4 T-lymphoid cell line, which lacks detectable CSF-1R transcripts, served as the negative control line in transcriptional assays.

cDNA cloning of the 5' ends of CSF-1R transcripts. The genomic loci encoding PDGF-R<sub>α</sub> and CSF-1R are shown in Fig 2. Eighteen independent cDNA clones extending to the 5' ends of BeWo CSF-1R transcripts were isolated by the RACE method. The 5' ends of the clones were clustered in genomic sequences contained within noncoding exon 1 (E1), located 26 kbp upstream of receptor coding sequences; these sequences were spliced to exon 2 sequences (E2) in each BeWo cDNA clone. By contrast, three cDNA clones isolated from monocyte RNA contained 5' ends from genomic sequences immediately contiguous to CSF-1R coding sequences. The nucleotide sequences of E1 and E2 and their 5' flanking sequences are shown in Fig 3. Our findings are consistent with results of Visvader and Verma<sup>15</sup> indicating that CSF-1R transcripts have separate origins in placental and monocytic cells.

Mapping of transcriptional initiation sites. S1 nuclease protection assays were performed to further delineate the initiation sites of CSF-1R transcription. A 309-bp genomic probe extending upstream from exon 2 was used to map the 5' ends of monocyte CSF-1R transcripts (Fig 4A). Transcripts were not detected in Molt-4 cells, but a single protected fragment of 183 bp was identified in BeWo RNA, consistent with the 5' splice acceptor junction previously identified in cDNA clones. Several protected fragments were identified when this probe was hybridized to monocyte RNA. At least three major and four minor transcription initiation sites were localized in the exon 2 region 3' to the placental splice acceptor; one minor site was located 17 bp 5' to the splice junction (Figs 4A and 3B). The monocyte start sites were located 95 to 197 bp 5' to the sequences encoding the translation initiation (ATG) codon. Protected fragments identified in RNA from TPA-treated U-937 cells were similar to those seen in monocytes, although there was a difference in the percentage of transcripts that originated from major or minor transcription initiation sites. The 5' ends of two of the three monocyte cDNA clones were indicated as dots below E1 sequences, and the placental CSF-1R transcription initiation sites determined by S1 analysis were indicated by arrows. In B, human Alu repeated sequences are overlaid, the 5' ends of monocyte cDNA clones are indicated as dots below E2 sequences, and the monocyte CSF-1R transcription initiation sites identified by S1 analysis are indicated by arrows. The placental E2 splice acceptor is indicated.
and six minor transcription initiation sites were evident within exon 1 sequences (Fig 4B). The 5' ends of 12 of the 18 BeWo cDNA clones coincided with the sites determined by S1 analysis (Fig 3A), and resided 412 to 509 bp downstream from the 3' end of the PDGF-\(R_a\) gene. Thus, in choriocarcinoma cells, CSF-1R transcription is initiated at several sites clustered within an exon separated by 26 kb from the first coding exon.

Promoter activity of the regions 5' to CSF-1R transcription initiation sites. Genomic fragments containing the separate origins of the placental and monocyte CSF-1R transcripts (Fig 2) were introduced in both orientations immediately upstream from the CAT gene in a promotorless and enhancerless plasmid, pCAT3M. To identify unequivocal transcriptional activity with these constructs, it was necessary to introduce an exogenous viral enhancer, the SV40 core enhancer, 3' to the CAT gene (pCAT/SV40). The promoter constructs were introduced into the model human cell lines, as well as NIH-3T3 fibroblasts, because the latter line is easily transfected and has been shown to support expression of many human genes.

A 0.55-kb Sac I fragment containing all of the CSF-1R monocyte transcription origins (Fig 3B) directed CAT expression in U-937 myeloid cells when inserted in the appropriate orientation in the pCAT/SV40 construct; functional activity was not evident in NIH-3T3, BeWo or Molt-4 cells (Fig 5, lane 5). Transcriptional activity was not identified when this fragment was inserted in inverse orientation relative to the CAT gene (Fig 5, lane 6).

A 0.77-kb BamHI fragment containing all of the CSF-1R placental transcription origins (Fig 3A) directed CAT expression in both BeWo choriocarcinoma cells and NIH-3T3 cells when inserted in the appropriate orientation in the pCAT/SV40 construct (Fig 5, lane 9); transcriptional activity was not evident in the other cell types. This fragment was capable of directing lower levels of CAT expression independent of the SV40 enhancer when introduced into NIH-3T3 cells (Fig 5, lane 7). Reporter gene activity was not detectable when this fragment was inserted in inverse orientation relative to the CAT gene (Fig 5, lane 10).

S1 nuclease protection analysis of RNA from transfected cells. To confirm that CAT gene expression resulted from correctly initiated transcripts, we analyzed RNA from transfected cells. CSF-1R/CAT fusion transcripts were not detectable by S1 nuclease assays, an observation consistent
Fig 5. CAT assays demonstrating the activity of CSF-1R promoter constructs in U-937 human myeloid leukemia, NIH-3T3 mouse fibroblast, BeWo human choriocarcinoma, and Molt-4 human lymphoid leukemia cell lines. A legend indicating the CSF-1R promoter fragments (see Fig 2 for locations) and their orientation relative to the CAT gene is shown below lanes 1 through 10. The presence of an exogenous SV40 enhancer is indicated 3' to the CAT gene in appropriate constructs. Each lane represents the average CAT activity standardized for p-galactosidase activity; CAT activity for each construct is expressed as a percentage of the positive control, pCMV CAT.

Comparison of promoter sequences. The sequences of the two promoter fragments were analyzed for structural features and putative binding sites of known transcriptional factors (Fig 3). Neither fragment contained classical promoter elements, such as TATA or CAAT boxes, or consensus sequences for Sp1 binding. The upstream 0.77-kb BamHI genomic fragment contained 209 bp of 3' untranslated nucleotides from the terminus of the PDGF-RE gene (Fig 3A). A potential binding site (A/T)GATA(A/G) for the major human erythroid DNA-binding protein GATA-1 was present in the PDGF-RE sequences. The intervening 412 nucleotides upstream of the most 5' placental CSF-1R transcription origin consisted of 61% C or G nucleotides. The consensus sequence for binding of basic helix-loop-helix (HLH) proteins (CANNTG) was present three times in these sequences; two of these potential sites conformed to a consensus sequence for E47 binding. The consensus sequence for myb binding (C/T)AAC(G/T)G was located 193 bp 5' to the placental splice acceptor. The noncoding E2 sequences from this region contained three additional PU.1 binding sequences.

To analyze the transcripts from the monocyte promoter, we hybridized RNA isolated from U-937 cells containing the 0.55-kb Sac I/SV40 construct with a probe derived from this plasmid. The 5' ends of the fragments protected by this probe coincided with the origins of endogenous gene transcripts previously identified in U-937 cells (Fig 6A), indicating that neo* RNAs were correctly initiated within the monocyte promoter. There were no appreciable differences among the protected fragments found in RNA harvested from U-937 cells treated with TPA; this result is consistent with data from previous nuclear run-on experiments indicating that TPA does not alter the endogenous CSF-1R transcription rate.

To study transcripts initiated within the placental promoter fragment, we hybridized a 1,108-bp probe containing the 0.77-kb BamHI genomic fragment with RNA from NIH-3T3 murine fibroblasts stably transfected with the 0.77-kb BamHI/neor/SV40 construct. The 5' ends of the protected fragments identified with this probe correlated with the endogenous transcription origins defined in BeWo cells (Fig 6B); hence, transcripts were correctly initiated within the CSF-1R placental promoter.

We identified two functional CSF-1R promoters by fusing genomic sequences to bacterial reporter genes and introducing the resultant constructs into human choriocarcinoma and myeloid leukemia cells. Nucleotide sequences located with results published for other promoters linked to CAT sequences. Because constructs containing the neo* gene have yielded stable transcripts detectable by RNA protection assays, the 0.55-kb Sac I and 0.77-kb BamHI fragments were introduced in appropriate orientation upstream of this reporter gene. The SV40 enhancer was inserted 3' to the CAT gene in appropriate constructs. Each lane represents the average CAT activity standardized for p-galactosidase activity; CAT activity for each construct is expressed as a percentage of the positive control, pCMV CAT.

DISCUSSION

We identified two functional CSF-1R promoters by fusing genomic sequences to bacterial reporter genes and introducing the resultant constructs into human choriocarcinoma and myeloid leukemia cells. Nucleotide sequences located
Fig 6. S1 nuclease protection assays confirming that transcripts of promoter constructs initiate correctly in stable transfectants. RNAs isolated from stably transfected cells were hybridized to the S1 probes shown below the panels and digested with S1 nuclease where indicated (+). The probe used in A is a 625-bp probe radiolabeled at a Bgl II site contained in the neo6 gene; this probe was linearized in sequences upstream of transcription initiation sites predicted for the monocyte promoter construct. A shows the major protected fragments (arrows) for untreated and TPA-treated U-937 human myeloid cells stably transfected with the monocyte promoter construct. The probe used in B is a 1,108-bp probe radiolabeled in neo6 sequences and linearized upstream of the predicted transcription initiation sites for the placental promoter construct. The arrows in B indicate the protected fragments found in NIH-3T3 mouse fibroblasts stably transfected with the placental promoter construct. DNA size markers are indicated.

The 5' ends of the CSF-1R transcripts expressed in BeWo choriocarcinoma cells arise from a 97-bp region positioned 15 to 30 bp 3' to the two transcript origins previously defined in normal placental cells and JEG-3 choriocarcinoma cells by Visvader and Verma.14 Our analysis of the 5' ends of monocyte and U-937 CSF-1R transcripts delineated several start sites spanning a region of 102 bp that contains the placental E2 splice acceptor, in contrast to the single transcription start site identified by Visvader and Verma for U-937 cells.14 We attribute these discrepancies to technical differences in analysis of CSF-1R transcripts. Whereas Visvader and Verma used classic primer extension methods, we used PCR to amplify cDNA products. A potential advantage of the latter procedure is that longer extension products containing the 5' ends of purine-rich CSF-1R transcripts can be selected, cloned and sequenced. These investigators also noted that single-stranded M-13 phage-derived probes from E2 hybridized weakly to CSF-1R transcripts. In our studies, classical end-labeled S1 nuclease protection probes yielded readily detectable CSF-1R-specific protected RNA hybrid fragments.

The upstream promoter apparently contains sequence elements necessary for transcription of the CSF-1R gene in placental trophoblasts and mouse fibroblasts, but not in myeloid or lymphoid cells. Although the placental CSF-1R promoter has a high GC content (61%), the sequence lacks potential binding sites (GC boxes) for the transcription factor Sp1, which are often found in promoters for housekeeping genes.47 Two potential binding sites for transcription factors are shared by the separate CSF-1R promoters: one is the consensus sequence (CANNTG) for basic HLH proteins.48 Transcription factors within this family may play a critical role in regulating cell differentiation; for example, expression of MyoD can induce myogenesis and expression of muscle-specific genes in various cell types.49 Potential binding sites (GAGGAA) for a second transcriptional activator protein, PU.1, are repeated four times within CSF-1R placental noncoding E1 sequences and three times...
within noncoding E2 sequences located in the monocyte promoter. Thus, CSF-1R transcripts initiated from the upstream placentomal promoter contain seven PU.1 boxes, whereas those from the downstream monocyte promoter may contain as many as three PU.1 elements.

CSF-1R transcription originating from the downstream promoter appears restricted to myeloid cells. Potential binding sites for two transcription factors that function in such cells include the CK-1 sequence element, which is found in the promoter region of several hematopoietic growth factor genes.45 CK-1 sequences specifically bind a nuclear transcription factor, NF-GMa, with differing affinities for sequence elements contained in the granulocyte/macrophage-CSF (GM-CSF), G-CSF, interleukin-3 (IL-3), and interleukin-5 (IL-5) genes.46 Although NF-GMa binding has been shown to activate transcription of promoter constructs transfected into embryonic fibroblasts,47 deletional analyses of both the human and mouse GM-CSF promoters failed to demonstrate a role of the CK-1 sequence element in either phorbol ester induction or basal-level transcription by T-cell nuclear transcription factor, NF-GMa, with differing affinities for sequence elements contained in the granulocyte/macrophage-CSF (GM-CSF), G-CSF, interleukin-3 (IL-3), and interleukin-5 (IL-5) genes.46 Although NF-GMa binding has been shown to activate transcription of promoter constructs transfected into embryonic fibroblasts,47 deletional analyses of both the human and mouse GM-CSF promoters failed to demonstrate a role of the CK-1 sequence element in either phorbol ester induction or basal-level transcription by T-cell lineages.48 The monocyte promoter also contains a single potential binding sequence for myb, a transcriptional activator expressed by myeloid cells.49 However, multiple copies of the myb binding sequence may be required to confer transcriptional activation, and only one such element is present in the CSF-1R monocyte promoter.50

The close proximity of the CSF-1R placental exon 1 to the PDGF-RA gene is provocative, but it is not clear how this linkage influences CSF-1R expression. Conceivably, transcription of PDGF-RA sequences may alter the activity of the placental CSF-1R promoter located between the two genes. Thus, the tandem organization of the receptor genes might underlie a mechanism for their mutually exclusive expression in different cell types of the developing placenta.

The CSF-1R monocyte and placental promoter constructs required insertion of an exogenous viral enhancer capable of activating heterologous cellular promoters to demonstrate unequivocal transcriptional activity in our transient expression assay. Because of the inherent limitations of the assay, we cannot directly correlate the observed CAT activity with the transcriptional rate of the endogenous CSF-1R gene. Hence, important regulatory elements within the CSF-1R gene may not have been included in the genomic fragments we have analyzed. By using promoter constructs that lack an exogenous enhancer as “enhancer traps,” genomic sequences can be screened to identify regulatory elements 5' or 3' to the respective transcription origins.

Exogenous factors may regulate CSF-1R cell surface expression in myeloid cells by both posttranscriptional and transcriptional mechanisms.54-56 CSF-1R expression is regulated posttranscriptionally by GM-CSF or IL-3 in a murine myeloid precursor cell line expressing GM, IL-3, and CSF-1 receptors.52 Similarly, TPA stabilizes receptor transcripts but does not alter CSF-1R transcription rate in human myeloid leukemic cell lines.53,55 By contrast, the macrophage activator lipopolysaccharide downregulates CSF-1R mRNA expression by decreasing transcription in murine macrophages.53 The promoter constructs and reporter gene assays defined in our studies can now be used to dissect the role of sequence elements immediately upstream of the transcript origins in monocytes in mediating the transcriptional component of CSF-1R regulation.

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