Identification of an Erythroid Active Element in the Transferrin Receptor Gene*

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The function of the cell surface transferrin receptor (TfR)1 (reviewed in Refs. 1 and 2) is to mediate cellular uptake of iron from a plasma glycoprotein, transferrin. Iron uptake from transferrin involves the binding of transferrin to TfR, internalization of transferrin within an endocytic vesicle by receptor-mediated endocytosis, and the release of iron from the protein by a decrease in the endosomal pH. After iron release from transferrin within endosomes, iron passes through the endosomal membrane via the endosomal Fe2+ transporter, Nramp2, also known as the divalent cation transporter (3). Virtually all the iron taken up by immature erythroid cells appears in heme, whose rate of synthesis is at least one order of magnitude higher than that in the liver, the second most active heme producer in the organism (4).

With the exception of mature erythrocytes and some other terminally differentiated cells, TfR are probably expressed on all cells, but their levels vary greatly with immature erythroid cells showing very high densities of TfR. Erythroid heme synthesis, which uses more than 80% of iron leaving plasma, is critically dependent on iron uptake mediated by high levels of TfR in erythroid cells (4). This is not only exemplified by numerous in vitro and in vivo models demonstrating that up-regulation of TfR levels during erythroid differentiation (5–9) but also by recent studies exploiting TfR knockout mice (10). Transgenic animals with no functional receptors die in utero, and mice containing only one functional copy of the TfR develop hypochromic microcytic anemia (10). Recently, a homologue of TfR, designated as TfR2, has been identified (11). Apparently, TfR2 is unable to compensate the loss of the “classical” TfR, which is highly likely indispensable for hemoglobinization.

During differentiation of erythroid cells, TfR mRNA and protein levels increase dramatically (4, 6–8). In most cell types, TfR mRNA expression can be enhanced by decreased cellular iron by a mechanism involving binding of iron regulatory proteins (IRPs) to the iron-responsive elements (IREs) of the 3′ untranslated region of the TfR, an interaction that stabilizes the receptor mRNA (reviewed in Refs. 4 and 12). However, TfR mRNA levels are only slightly affected by changes in iron levels in hemoglobin-synthesizing cells (6), and IRP activities remain virtually unchanged during erythroid differentiation (7). These findings suggest that TfR expression is regulated differently in erythroid and nonerythroid cells. In fact, high levels of receptor expression are associated with transcriptional up-regulation of the mRNA levels in almost all erythroid systems examined (6–8). Therefore, it appears that developing erythroid cells evolved a transcriptional mechanism that can override the ubiquitous IRE/IRP control of TfR expression.

The mechanisms involved in the basal and cell proliferation-dependent transcription of TfR expression have been partially characterized (12–16). About 100 base pairs upstream of the transcription start site is required for driving the transcription. Regulatory elements involved include the AP-1/cyclic AMP-responsive element (CRE)-like, SP-1/GC-rich sequences, and...
the recently identified hypoxia-response element (17, 18). However, little is known about the transcriptional mechanism of the receptor expression in developing erythroid cells. The rate of transcription of TfR correlates well with that of erythroid heme synthesis and remains elevated in nonproliferating erythroid cells such as differentiating murine erythroleukemia cells (MEL) (7) and chicken embryonic erythroblasts (6). Therefore, the transcriptional regulation of TfR in differentiating erythroid cells seems to be distinct from that in proliferating nonerythroid cells.

The active transcription of TfR appears to be one of the essential molecular mechanisms required for efficient hemoglobin synthesis in the course of erythroid development. We have analyzed the regulation of TfR promoter activity in MEL cells that can be induced to undergo erythroid differentiation, including the up-regulation of TfR expression. We report here that a promoter region containing a linked Ets-binding site (EBS) and CRE-like motif is critical for the transcriptional activation of TfR expression. These data indicate that the TfR promoter is erythroid active and mediates inducible transcription upon induction of hemoglobinization.

**EXPERIMENTAL PROCEDURES**

**Plasmids and Synthetic Oligonucleotides**—The fusion gene construct of the TfR promoter-luciferase reporter was prepared by subcloning a polymerase chain reaction fragment of the human TfR promoter region (−282 to +14) into the pGL2 Basic vector (15). The deletion construct (−118 to +14) was made by removing a Sma I fragment of the (−282 to +14) plasmid. Mutations of the putative regulatory elements were generated by a unique site elimination mutagenesis kit (Amer sham Pharmacia Biotech). The mutagenesis primers and the sense strands of the oligonucleotides used in EMSAs were as follows.

| TR [–87 to –56] Wild type | 5′-CGT GCC TCA GGA AGT GAC GCA CAG CCC CCC TG-3′ |
|--------------------------|-------------------------------------------------|
| TR [CREm]                | 5′-CGT GCC TCA GGA AGT cga cCA CAG CCC CCC TG-3′ |
| TR [EBSm]                | 5′-CGT GCC TCA GGC cGT GAC GCA CAG CCC CCC TG-3′ |
| TR [EBS Crem]            | 5′-CGT GCC TCA GGC cGT cga cCA CAG CCC CCC TG-3′ |
| TR [–72 to –25] Wild type | 5′-GAC GCA CAG CCC CCC TGG GGG CCG GGG GGG CCC GCA GGC TAT AAA CCG-3′ |
| TR [GCM]                 | 5′-GAC GCA CCT asc TGG taa CCG cta cta GtG CCA GGC TAT AAA CCG-3′ |

The oligonucleotides harboring consensus *cis*-acting elements were from either Promega or Santa Cruz Biotechnology.

**Cell Culture**—MEL cells were grown in Eagle's minimal essential medium supplemented with 10% fetal bovine serum and 2 mM glutamine. To induce erythroid differentiation, cells were seeded at 1 × 10⁵ cells/ml in medium containing 1.5% Me₂SO or 5 mM HMBA for 60 h. The hemoglobin content was checked with benzidine staining.

**In Vitro Nuclear Transcription of TfR**—Nuclear run-on assays were employed to detect the amounts of initiated TfR transcripts in uninduced and Me₂SO-induced MEL cells. MEL cells were induced to differentiate into hemoglobin-synthesizing cells in the presence of 1.5% Me₂SO for 60 h. Control cells were untreated for the same period. Equal amounts of labeled nascent transcripts purified from the nuclei were hybridized with immobilized cDNA probes for TfR, β-globin, erythroid 5-aminolevulinate synthase, and β-actin as described (7).

**RESULTS**

In *Vitro Nuclear Transcription of TfR*—Nuclear run-on assays were employed to detect the amounts of initiated TfR transcripts in uninduced and Me₂SO-induced MEL cells. MEL cells were induced to differentiate into hemoglobin-synthesizing cells in the presence of 1.5% Me₂SO for 60 h. Control cells were untreated for the same period. Equal amounts of labeled nascent transcripts purified from the nuclei were hybridized with immobilized cDNA probes for TfR, β-globin, erythroid 5-aminolevulinate synthase, and β-actin. Fig. 1 shows that the rate of transcription of TfR, as well as the erythroid-specific genes, β-globin and erythroid 5-aminolevulinate synthase,
markedly increased in Me₂SO-induced cells, whereas that of β-actin increased only slightly. These results indicate that the transcription of TfR is significantly activated upon induction of differentiation. It should be pointed out that after 60 h of incubation, proliferation has already stopped in both induced and uninduced cells. Therefore, the activation of TfR transcription in induced cells is associated with the erythroid differentiation program rather than with proliferation status.

Functional Analysis of the TfR Promoter—To identify the regulatory gene elements involved in TfR up-regulation in MEL cells, a fusion gene construct linking the TfR promoter region (−282 to +14) (Fig. 2) and a luciferase reporter gene were prepared and transiently transfected into MEL cells. Luciferase assays were performed with cell extracts from uninduced and induced MEL cells. As shown in Table I, TfR promoter activity was enhanced 6–8-fold in cells induced to differentiate either by Me₂SO or HMBA. This stimulation is well correlated with the degree of induction as observed from nuclear run-on assays. As the stimulation of TfR promoter activity can be observed with two structurally unrelated differentiation inducers, which act through different mechanisms (20), this effect is erythroid differentiation-dependent rather than being caused by nonspecific perturbation because of these agents. The activities of several viral transcription units including SV40, Rous sarcoma virus, and human immunodeficiency virus, type I were also tested but these did not exhibit any increase in activities upon Me₂SO induction (Table I). These results indicate that the stimulation of TfR promoter activity is likely a specific event during Me₂SO-induced differentiation. We have also transfected the TfR promoter into NIH 3T3 fibroblasts, and no induction of promoter activity was observed when Me₂SO was added (data not shown), suggesting that the stimulation of TfR promoter activity in differentiating MEL cells is an erythroid-specific event.

Several deletions and mutations were introduced into the TfR promoter to identify the regulatory elements involved in the transcriptional activation in induced MEL cells (Figs. 2 and 3). Deletion from −282 to −119 did not appreciably affect TfR promoter activity (Fig. 3). In the region from −118 onwards, there are several putative regulatory elements (Figs. 2 and 3). A sequence AGGAA matches perfectly with the consensus EBS (21). Adjacent to the EBS is a sequence TGGCGCA that is similar to both AP-1 (TGACTCA) and CRE (TGACGTCA) (22). In addition, a long GC stretch, which contains a consensus SP-1 sequence, is located between the AP-1/CRE-like site and the TATA box. Elimination of the EBS (TR [EBSm]) significantly inhibited the inducible promoter activity (Fig. 3). Likewise, mutation of the AP-1/CRE site (TR [CREm]) or simultaneous disruption of both EBS and AP-1/CRE site (TR [EBS CREm]) abolished almost all inducible promoter activity (Fig. 3). As retaining either the EBS or the AP-1/CRE-like sequence is not sufficient to confer the normal inducible promoter activity, it seems that both EBS and AP-1/CRE site may cooperate in the stimulation of TfR promoter activity in MEL cells. Alternatively, because simultaneous mutation of the EBS and AP-1/CRE sequences leaves the GC-rich/SP-1 sequence intact, this also indicates that the GC-rich/SP-1 sequence alone is not sufficient to mediate the inducible transcription. In fact, extensive disruption of the GC-rich/SP-1 sequence (TR [Gcm]) adjacent to the CRE-like sequence did not appreciably affect the inducibility of promoter activity (Fig. 3).

DNA-Protein Binding at the Linked EBS and AP-1/CRE-like Region—In parallel with the reporter gene assays, EMSA was performed to identify the potential DNA-binding factors that interact with the critical elements. Using an oligonucleotide harboring the TfR promoter sequence (TR [−87 to −56], which contains the EBS, AP-1/CRE-like element, and part of the GC stretch) as the probe, at least five major DNA-binding factors (A–E) were identified in uninduced and induced MEL nuclear extracts (Fig. 4). Several reproducible changes in the pattern of the DNA-protein complexes were observed. 1) A distinct complex C was more apparent in the nuclear extracts prepared from induced cells. 2) A decrease in complex E was observed in nuclear extracts obtained from induced cells. 3) Careful resolution of these complexes revealed that complex B in nuclear extracts prepared from induced cells had a faster mobility than that from uninduced cells. Importantly, these patterns are reproducible using two differentiation inducers, Me₂SO and HMBA.

To characterize the DNA-binding factors at the TfR promoter region, a panel of oligonucleotides harboring consensus recognition sequence for transcription factors was used for competition EMSA (Fig. 5, A and B). These oligonucleotides were capable of binding to putative transcription factors that regulate the TfR promoter (Fig. 5B). Stimulation of binding activity of the erythroid-specific transcription factor, NF-E2 (23), in induced cells serves as a marker of induction of differentiation (Fig. 5B). The pattern of DNA-protein complexes identified using the TfR promoter oligonucleotide probe (Figs. 4 and 5A) was very similar to that using the consensus CRE oligonucleotide (Fig. 5B). In fact, formation of the majority of DNA-protein complexes (A–E) can be effectively prevented by a 100-fold excess of the CRE oligonucleotide (Fig. 5A, lanes 3). However, the same excess concentration of two highly related oligonucleotides, AP-1 and NF-E2, did not appreciably affect the DNA-protein binding (Fig. 5A, lanes 4 and 5). These results suggest that the AP-1/CRE-like sequence in the TfR promoter behaves more like a CRE in MEL cells in terms of protein binding. Furthermore, the addition of an antibody against the DNA-binding and dimerization domain common to both ATF-1 and CREB-1 resulted in supershifting of most of the DNA-binding factors to the TfR promoter oligonucleotide (Fig. 5C). In contrast, an anti-AP-1 (Jun) antibody has no effect on the DNA-protein complexes. These results indicate that ATF/CREB-like factors, rather than AP-1 (Jun), can bind to the AP-1/CRE-like sequence in the TfR promoter. Previous studies have indicated that in inducible MEL cell clones, the AP-1 (Jun) expression is hardly detected during the course of induced differentiation (24).

When excess consensus EBS oligonucleotide was incubated with the binding mixtures, complexes A and E were clearly abolished (Fig. 5A, lanes 2 and 9). Because formation of these complexes can be prevented by both consensus EBS and CRE oligonucleotides, they are likely comprised of both EBS- and CRE-binding factors. Interestingly, a new complex (F) appeared when consensus CRE oligonucleotide was used as a competitor to remove the CRE-binding factors from the binding reaction (Fig. 5A, lanes 3 and 10). The mobility of complex F was identical to the one that appears when consensus EBS

![FIG. 1. Stimulation of TfR gene transcription in differentiating MEL cells.](image)
The TfR promoter region. Part of the promoter region containing the putative cis-acting elements (underlined) is shown. These elements were aligned with the consensus transcription factor recognition sequences to show the sequence similarities (denoted by italics). Nucleotide numbers are denoted with the transcription start site assigned as +1 (13).

**TABLE I**
Stimulation of TfR promoter activity upon induction of differentiation of MEL cells

|                             | MeSO   | HMBA   |
|-----------------------------|--------|--------|
| TR [-282]                   | 7.0 (1.5) | 6.8 (1.2) |
| SV-40                       | 1.0 (0.2) | 1.1 (0.2) |
| Rous sarcoma virus          | 1.5 (0.2) | N.D. |
| Human immunodeficiency virus| 1.3 (0.3) | N.D. |

DISCUSSION

The TfR is a cell membrane-associated glycoprotein that serves as a gatekeeper in mediating and regulating cellular uptake of iron from transferrin (1). It is now well established that in proliferating nonerythroid cells, TfR expression is regulated at the post-transcriptional level by intracellular iron through IREs localized in the 3'-untranslated region of TfR mRNA (reviewed in Refs. 1, 4, and 12). IREs are recognized by IRPs, which when intracellular iron levels are scarce, bind to the IREs of TfR mRNA preventing its degradation. On the other hand, the expansion of the labile iron pool inactivates IRP-1 binding to the IREs (1, 12) and leads to a degradation of IRP-2 via a ubiquitin-proteasome pathway (25–27), resulting in a rapid decay of TfR mRNA. However, erythroid cells, which are the most avid iron consuming cells, evolved mechanisms that can override the IRE/IRP control of TfR expression (4). Data obtained from several laboratories indicate that during erythroid differentiation TfR is regulated at the transcriptional level (6–8) and that the IRE/IRP system is probably not involved in receptor up-regulation (6).

In the current study, we demonstrated that the TfR promoter activity is specifically activated during induced MEL cell differentiation, in agreement with *in vitro* nuclear transcription studies using run-on assays. Previous studies have pointed to
the involvement of a promoter region of ~100 base pairs in TfR transcription in proliferating nonerythroid cells (12–16). Here, we demonstrated that the same region can also confer a significant enhancement of promoter activity in nonproliferating, hemoglobin-synthesizing MEL cells.

Our study clearly demonstrates that the composite EBS and AP-1/CRE-like region is critical for the induction of TfR promoter activity in differentiating MEL cells. Previous studies have showed that the Ets may be involved in the transcription of TfR. For instance, retroviral expression of Ets-1 was shown to enhance TfR protein expression and stimulate hemoglobinization in K562 and HEL cells (28). Moreover, Sieweke et al. (9) demonstrated that transfection of Ets-1 is able to induce 2–3-fold increase in TfR promoter activity in fibroblasts. Here, our data indicate that the EBS of the TfR promoter is essential for stimulation of transcription in an inducible erythroid cell line. Although we were unable to detect Ets-1 in supershift assays using commercially available Ets-1 antibodies (data not shown), this does not exclude the possibility that the EBS-binding factor identified in our gel shift assays is one of the Ets family of transcription factors that has a function similar to Ets-1 (21).

Most EBS are usually found to be linked with other cis-acting elements, and the Ets family of transcription factors often appears to require cooperation with other factors for their activities (21). Further to identification of EBS as an essential element for the induced TfR transcription in erythroid cells, our data also pointed to the involvement of an AP-1/CRE-like site, which is just one base pair adjacent to the EBS. Supershift EMSA demonstrated that the AP-1/CRE-like site recognizes CREB/ATF-like factors. Mutation of this site significantly inhibited the erythroid differentiation-induced TfR promoter activity. The binding of the CREB/ATF-like factors to the AP-1/CRE-like site is constitutive in both uninduced and induced...
MEL cells. However, a shift in the pattern of DNA-protein binding exists following MEL cell induction. Hence, changes in the binding activities of selected CREB/ATF family members or post-transcriptional modification of these factors (22) are attributable to the inducible TfR promoter activity. It is possible that these CREB/ATF family members, presumably with different transactivation activities, may compete for the CRE-like site and elicit the resulting promoter activity in a tissue- or stage-specific manner.

Previous reports have indicated that the AP-1/CRE-like sequence of the TfR promoter may also be important in cell growth-dependent TfR gene transcription (13–16). The identities of the trans-acting factors on the AP-1/CRE-like sequence are largely unknown, but they appear to be distinct from the CREB/ATF-like factors we have demonstrated in this report. A large number of AP-1/CRE sites of various genes have been identified to mediate gene transcription in cell growth and differentiation (22). Interestingly, the AP-1/CRE-like sequence (TGACGCA) of the TfR promoter is the same as a regulatory element of the c-fos promoter termed the fos-AP-1 site (29). Functional analysis of the isolated fos-AP-1 site revealed cell type-specific transcriptional properties (29). Therefore, it is possible that the AP-1/CRE-like sequence of the TfR promoter may also possess similar properties in mediating a wide range of transcriptional regulation of TfR in response to cell growth in general, and also during differentiation of some cell types, particularly, the developing erythrocytes.

Although additional regulatory elements may be present elsewhere in the 5′-region, our study clearly demonstrates that the composite EBS and AP-1/CRE-like region is critical for the induction of TfR promoter activity in differentiating MEL cells. It is likely that apart from its role in the transcriptional regulation of TfR in erythroid cells, the Ets and CREB/ATF factors may also play a role in erythroid differentiation-dependent expression of other genes harboring EBS and/or AP-1/CRE elements. The first identified member of the Ets family of transcription factors was the v-Ets, the causative component for erythroleukosis of avian erythroleukosis virus E26 (21). The cellular homologue, Ets-1, is able to stimulate erythroid differentiation, presumably by mediating the transcription of the heme synthesis enzyme porphobilinogen deaminase (9), the erythroid transcription factor GATA-1 (30), and TfR (this report and Ref. 9). On the other hand, some studies have implicated the possible participation of AP-1/CRE sites in erythroid differentiation-dependent gene expression. For example, AP-1-like elements, including the NF-E2 binding sites, have been identified in enhancers of various globin genes (31, 32). Moreover, the promoter of the adult form of the transcription factor NF-E2, which controls the expression of a number of erythroid genes such as globin and porphobilinogen deaminase, has been shown to contain a putative CRE (33). Interestingly, the ferri-TfH subunit gene transcription is enhanced during erythroid differentiation of MEL cells, and this is mediated at least in part by an AP-1-like sequence (34), which may be recognized by the abundant CREB/ATF factors in MEL cells. The up-regulation of TfR in hemoglobin-synthesizing cells via a specific transcriptional mechanism may reflect a tight coordination between expression of TfR and most erythroid-specific genes, which are transcriptionally regulated during erythroid differentiation.

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